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SECTION OF BIOLOGY*

A GENETIC APPROACH TO A STUDY OF INFLUENZA VIRUSES†

By FRANK M. BURNET‡

Quite apart from its academic interest, variation in viruses is a matter of high practical importance. Immunization against yellow fever, for instance, depends on the use of a particular variant of the natural pathogenic virus, which has lost its capacity to produce serious lesions and retains its immunizing powers. In an entirely different direction, we have the appearance in 1918–19 of an influenza epidemic or series of epidemics almost certainly due to strains of influenza virus derived by some mutational process from less virulent preceding strains.

In recent years, geneticists have become increasingly interested in the phenomena of reproduction mutation and survival in microorganisms even where these show no obvious evidence of bisexual reproduction. There is much in the literature dealing with mutation and recombination of characters in yeasts and fungi such as *Neurospora* with a very simple type of sexual reproduction, and there is more limited recent work on the possibility of recombination of characters in bacteria and bacterial viruses. This lecture is concerned with the possibility of a similar genetic approach to the problems that arise in the study of influenza viruses.

The group of viruses comprising the influenza virus and the viruses of mumps, Newcastle's disease, and fowl plague is a particularly convenient one for study. The viruses can be propagated in the cavities of the developing chick embryo, the infected fluid providing a very convenient source of virus. They can be liberated *in vitro* by simple methods based on their capacity to agglutinate red cells. Furthermore, a considerable range of differential characters can also be defined by suitable modifications of haemagglutinin reactions.

The essentials for any type of genetic study are two. The first is that the virus should be obtainable in the form of a pure clone, *i.e.*, as an infected embryonic fluid containing a population of virus particles derived from a single individual particle and, except for the occurrence of such mutants as appear in the course of virus growth during one process of infection, of uniform character. The second requirement is the characterization of each such pure clone by as many convenient methods as possible, so as to provide, for any experimental series of virus strains, a series of "genetic markers" that can be followed in mutation or recombination studies.

Pure clones in the sense defined are obtainable for any influenza virus that is sufficiently well adapted to growth in the allantoic cavity to allow a clear-cut fifty per cent titration end point. All that is required is to make all experiments with fluids produced by infecting embryos with limiting infective dilutions, *i.e.*, with fluid diluted to such an extent that only fifty per cent or less of the embryos used become infected. A strain of virus adapted for a long series of passages to an unusual tissue environment (mouse brain) may be grown readily in the allantoic cavity of the chick embryo. The fluid obtained is capable of producing fatal infection in the mouse brain and has several *in vitro* characters that differentiate it sharply from all normally encountered types of influenza virus. If such a virus is transferred successively from one embryo to another using virus at low dilution (1:100), there is a fairly rapid change in character toward the normal type of influ-

* The Section of Physics and Chemistry held a meeting on October 3, 1950, at which Doctor Theodore Shedlovsky, Rockefeller Institute for Medical Research, presented a paper entitled *Protochemical Cells*, illustrated with lantern slides. No abstract of this paper has been received.

† This paper, illustrated with lantern slides, was presented at a Special Meeting of the Section of Biology on October 5, 1950.

‡ Director, Walter and Eliza Hall Institute, Melbourne, Australia.

General
Early
direct

enza virus propagated in the chick embryo. If transfer is made consistently at limiting infective dilution, no change in the character of the virus occurs.

At each transfer, any mutants which may have appeared are eliminated by the use of a high dilution, in which there is only a minimal chance of any but the dominant original type of virus being present. The fact that continuous passage of a virus can be accomplished by this method in a new alien host, without the occurrence of adaptive change, provides a formal proof that adaptive change to a form characteristic of the new host is due to a combination of a quality shown by no other influenza virus strain. If a constant small amount of Neuro-WS virus is mixed with falling tenfold dilutions of a non-neurotropic influenza virus strain of different serological subtype, such as MEL, and the mixtures injected intracerebrally in mice, results such as those shown in TABLE 1 are obtained.

The failure of symptoms to appear in mice receiving large amounts of the non-neurotropic strain is a typical manifestation of interference between two viruses. If the mice concerned are killed six days after inoculation, when the control animals are dying, no virus is isolated from brain emulsions. The mice dying at the usual time (shown to the right of the table) give brain emulsions containing large amounts of Neuro-WS virus. Where interference is just breaking down in the group, N-WS 10^{-3} + MEL 10^{-2}, the brains contain relatively small amounts of virus. If a suitable amount of anti-WS ferret serum is added to the brain emulsion, no N-WS virus will grow when dilutions are inoculated into chick embryos. Any virus, however, which possesses the properties (a) of being able to persist for six days in the mouse brain and (b) of not being inactivated by anti-WS immune serum, will be isolated.

TABLE 1

INTERFERENCE BETWEEN NEURO-WS AND MEL INFLUENZA VIRUSES

Constitution of mixtures

N-WS	10^{-3}	10^{-2}	10^{-3}	10^{-3}	10^{-3}
MEL	10^{0}	10^{-1}	10^{-2}	10^{-3}	nil
Mice* (intracerebral injection)	–, –, –, –	–, –, –, –	8, 7, –, –	6, 6, 7, 7	5, 6, 6, 6

* —, Survival of mouse to 14 days; numbers indicate day mouse died.

mutation and selective survival of a mutant form which eventually overgrows the original.

Recombination experiments with influenza viruses have been designed as far as possible to imitate the conditions that have been successful in studies of bacterial virus recombination made by Delbruck and Luria, Hershey, and others. The requirement is to provide conditions by which a single cell can be infected by particles of two viruses, X and Y, carrying at least two easily distinguishable genetic markers, Ax Bx and Ay By. Following infection, it is also necessary to arrange conditions so that neither X nor Y will be reisolated, but that one possible recombinant, *e.g.*, Ax By, if it is formed, will be able to survive and multiply. A particular experimental combination has been found to be particularly suitable for such experiments. The strain Neuro-WS, produced in 1938 by Stuart-Harris, retains the serological character of the influenza A strain WS but is highly virulent for mice by intracerebral infection,

It has been found, with considerable regularity, that those mice in which partial interference is manifest give a virus which, after purification by the "pure clone" technique, is capable of producing fatal encephalitis in mice and has the serological character MEL. Experiments of the same type, in which the Neuro-WS strain was mixed with non-neurotropic strains of the other serological subtypes, SW., A′, and a

heat-stable strain of WS, all gave similar recombinants, in which the neurotropic quality of Neuro-WS was associated with the serological or other quality characteristic of the second non-neurotropic component. From three to five examples of each type of recombinant were obtained. These results are reported in detail in a series of papers to be published.*

At the present time, any interpretation of these results must be based on analogy with the much more exhaustively studied bacterial virus recombinations. We can see no reasonable alternative to the assumption that there are genetically significant subunits derived from the virus which, in the susceptible cell, duplicate virtually independently. At a late stage in the process, new aggregates of each necessary type of genetic unit are formed from the "pool," and these reconstitute the phenotypic expression of the virus, the "infective particles." This is, at present, no more than a working hypothesis, but it is one which is very stimulating in ideas for an experimental approach to problems of interference of virus latency, as in herpes simplex infections, and of the production in certain infections of soluble virus antigens and noninfective "partial virus."

* BURNET, F. M. & P. E. LIND. J. Gen. Microbiol. In press.

THE ROLE OF BLOOD PLATELETS IN THROMBOEMBOLISM*

By SYLVAN E. MOOLTEN†

While the bulk of a large thrombus of the bland type which may form in the veins after operation consists of ordinary blood clot, it is generally agreed that its incipient stage is an occlusive mass of sticky agglutinated platelets (white thrombus). Our concern is primarily with the factors which govern the number and adhesiveness of blood platelets and their affinity for a selected endothelial surface. The rate and extent of clotting which occurs in the column of trapped blood and its ultimate resolution, fibroblastic organization, or dislodgment as an embolus are crucial questions affecting the further evolution of a thrombus, but only after the phase of platelet deposition.

Role of Blood Platelets in Vascular Physiology. In a broad sense, the blood platelets occupy the central role in hemostasis. The primary event in hemostasis which follows injury to a blood vessel is plugging of the defect by agglutinated platelets well in advance of clotting. Lysis of part of these platelets releases vasoconstrictor substances into the vicinity of the defect. The speed and quality of subsequent clotting in the extravasated blood also depend upon the behavior of the platelets. Activation of thromboplastin has been attributed to platelet lysis, which provides also a large part of the accelerator substances which influence the rate of conversion of prothrombin to thrombin. Finally, platelets are intimately concerned with the anchorage and retraction of fibrin clot about the vascular defect as reinforcement and as matrix for fibrous union.

Parallelism Between Hemostasis and Thrombosis. Platelet agglutination and adhesion followed by clotting of whole blood and retraction of clot are common to both hemostasis and thrombosis. The latter is, in a sense, a magnified hemostasis. Inspection of thrombosed blood vessels *in situ* regularly discloses the tell-tale white thrombus to which the red thrombus above and below owes its initiation and anchorage. Firm contact of red thrombus with the vessel wall is favored by vasoconstriction and is made permanent by organization. In a vein, the latter gives rise to the local symptoms of phlebitis. If clot retraction occurs quickly, detachment of the red thrombus from its platelet anchorage may result in embolism.

Safeguards Against the Red Thrombus. Counteracting influences may include fibrinolytic ferments, which favor resolution

* This paper, illustrated with Kodachrome slides, was presented at the Regular Meeting of the Section of Biology on October 9, 1950. The research for this paper was aided in part by a grant from the National Heart Institute, United States Public Health Service.

† Director of Laboratory, St. Peter's General Hospital, New Brunswick, New Jersey.

of red thrombi in whole or in part, anticoagulant substances such as heparin or its natural counterpart, antithrombin, or the hypoprothrombinemia of vitamin K deficiency or that following dicumarol. Another protective factor is rapid blood flow; hence the smaller incidence of occluding thrombi in arteries than in veins, despite more frequent disease of the arterial wall. In spite of this, large white thrombi can form within the cardiac chambers, upon valve edges, or on the wall of the aorta.

Localization of the White Thrombus. Bizzozero (1882), who was familiar with the fact that white thrombus consisting of platelets preceded clotting *in vivo* and that fibrin became attached to the vessel wall only at the site of previous platelet deposit, intimated that the problem of thrombosis in man might better be studied in the behavior of the blood platelet than in the excessive coagulability of the blood or inflammation of the vessel wall, as previously theorized by Virchow. Others confirmed and amplified his work, with emphasis on factors which favor the silting out of platelets, *e.g.*, eddy formation at sites of projection within, or narrowing of, the lumen and sluggishness of blood flow. Thrombi were produced experimentally by mechanical, chemical, or thermal injuries to blood vessels or by insertion through their wall of foreign objects of fiber, metal, or glass. Nevertheless, no well-authenticated evidence of histologically demonstrable endothelial change has been reported in cases of bland venous thrombosis in man (Aschoff).

A physico-chemical change involving surface forces of a nature incapable of demonstration by ordinary histologic techniques remains an interesting possibility. In addition to their prompt clumping about the edges of a vascular defect in the first stage of hemostasis, the blood platelets readily adhere to foreign surfaces, such as glass, quartz particles, carbon particles, and bacteria, or agglutinate in the presence of foreign colloids or of plasma colloids which have been altered by addition of a variety of chemical substances, including freshly added heparin. Lampert (1931) attempted to correlate platelet adhesion with wettability of an endothelial or foreign surface to water (or blood). It has long been recognized that normal vascular endothelium preserves blood in fluid form and resists staining by the blood (Freund). Exposure of the blood vessels in a rabbit's mesentery to a bright photographic light immediately after death of the animal can be shown to alter the appearance of injected air bubbles. When it is first examined, a mild concavity is seen at the interface between air and blood. With the passage of time, the concavity becomes much sharper, as the wall becomes wetted with blood and separates the air bubble from its contact with endothelium. Application of alcohol or formalin to the exposed adventitia of a rabbit's inferior vena cava quickly induces blood staining of the corresponding area of intima and, if the animal is permitted to survive 24 hours, regularly induces a white thrombus with or without total occlusion by superimposed red thrombus. Whether this change in endothelium can be considered equivalent to a change from a "nonwettable" surface such as paraffin or silicone to a highly wettable surface such as glass is problematical. Our present interpretation is based on a theory of electrical charges whereby the interfacial tension between blood and endothelium is normally somewhat less than the surface tension of blood. Injury to the vessel wall causes reversal of endothelial charge and consequent "wetting" with attraction of platelets.

The supposition is reasonable that the same principles govern thrombus formation in man. Change in endothelial properties probably accounts for thrombosis at the site of atherosclerotic plaques in the major arteries and aorta. A similar change may account for thrombosis complicating prolonged spasm of an artery, as in Raynaud's disease or ergotism. Pressure upon deep veins in the calf muscles during prolonged lying upon a hard mattress has been cited as an initiating factor in postoperative venous thrombosis. Mural thrombi of the car-

diac chambers and valvular vegetations can be similarly interpreted in terms of endothelial wettability induced by ischemic necrosis or inflammation. The increased tendency to thrombosis reported in patients receiving digitalis may result from surface-active saponins in crude digitalis (Hueper).

Role of Platelet Number and Adhesiveness. Once local conditions in an endothelial surface have determined the formation of a white thrombus, its rate of growth and ultimate size will of necessity depend upon the number and adhesive quality of platelets swept into contact with the attracting site. Attempts have been made to correlate high platelet counts with the tendency to thrombosis, but, with the exception of cases of extreme thrombocytosis (thrombocythemia), the results have not come up to expectation. Much better correlation has been shown in the case of platelet adhesiveness, measured by the number and size of platelet clumps in a test sample of blood or plasma or by the rate of adhesion of platelets to a glass surface. The rotating glass tube method of H. P. Wright measures the rate of loss of platelets from contained blood within a certain time (90 minutes). The glass-wool filter of the writer and his associate, Leo Vroman, measures the number of platelets lost within a very short time (30 seconds) to a relatively enormous surface. A sample of citrated blood (1 c.c.) is dripped into a prepared wick of braided glass-wool and washed through with an excess of saline-citrate eluent. Erythrocyte and platelet counts are compared in the control sample and in the washings after correction for dilution. In the normal nonfasting subject, the range of adhesive platelets has been found to lie between 60,000 and 110,000 per cu. mm. (total count ranging between 200,000 and 350,000).

Increased platelet adhesiveness to glass-wool has been found regularly by us in patients convalescing from surgical or accidental trauma, including fractures, in cases of ischemic necrosis (myocardial infarction, peripheral vascular gangrene) and extensive soft tissue inflammation (cellulitis, widespread dermatitis), and in cancer. Total platelet counts were also elevated, but in a less consistent manner.

Platelet hyperadhesiveness proved diagnostically useful in certain cases of myocardial infarction, where it aided clinical differentiation from uncomplicated angina pectoris at a time when electrocardiographic changes had not yet become decisive. In proved cancer, hyperadhesiveness was found so regularly that suspicion of hidden cancer was aroused in certain cases in which no other objective finding was obtainable. In cancer, too, total counts were less consistently elevated. The high incidence of thrombosis as a complication of cancer, hitherto inadequately explained, is perhaps worthy of more extended study in terms of platelet behavior along these and related lines.

Preclinical Detection of Thrombosis. Although individual tests of platelet number and adhesiveness may aid in uncovering the predisposition to thrombosis, it is vastly more important to learn the moment at which such an unfortunate event actually commences. The latter is rarely if ever detectable by physical signs or by the patient's symptoms. Changes in platelet count and adhesiveness determined by serial tests may be helpful in detection of large thrombi in their early stages. Mural thrombosis in the wake of myocardial infarction has been suggested in a number of our cases by rapid drop in platelet count, especially adhesive platelets, corresponding to withdrawal of large numbers of more adhesive platelets from circulation to build white thrombi, as proved later by autopsy. Similar observations have been made in early venous thrombosis. Unexpectedly low initial count and adhesiveness proved to have similar meaning. In one case of widespread thrombosis complicating cancer of the stomach, post-thrombotic thrombocytopenia became so profound that actual purpura resulted.

Changes in Blood Coagulability. Clotting factors have been reported by competent observers to show changes reflecting thrombus formation, although not all such studies

are in agreement. Increased coagulability measured in clotting time has been described in whole blood, plasma, or diluted plasma with or without added thromboplastin or in the face of clot-retarding agencies such as heparin or silicone-coated containers. Comparison studies of some of these tests and the glass-wool test of platelet adhesiveness appear to show a correspondence such as might easily be explained by increased platelet lysis. Quick's theory of a chain reaction, in which platelet lysis accelerates thrombin formation from precursor elements and, in turn, thrombin accelerates platelet lysis, centers attention upon the platelets as principal catalysing agents in the initiation and completion of clotting. The rapid clotting of extravasated blood about a torn vessel, which is attributable to clot-accelerating factors liberated from the massed platelets which fill the defect, is paralleled by the finding that the venous return from a limb harboring a thrombus exhibits greater coagulability than blood from another limb. One might readily imagine that as long as blood continues to flow past a developing white thrombus it will acquire greatly enhanced clotting properties. Once the flow becomes completely arrested by the white thrombus, clotting will quickly occur *en masse*.

Although one might suppose as a corollary that the coagulability of blood returns to normal when the site of thrombosis is completely sequestered by clotting, a number of cases of thrombosis have come to our notice in which a sharp drop in prothrombin level was observed. We are inclined to regard such abrupt prothrombin decline as a warning signal of thrombosis equal in importance to a rapid drop in adhesive platelet count. Possibly, prothrombin is withdrawn from circulation in the formation of red thrombus, perhaps by its consumption to form thrombin (Quick) or by its adsorption upon fibrin.

A rapid fall in prothrombin level in patients receiving dicumarol may thus cause perplexity. It may be the sought for drug response. On the other hand, it may reflect therapeutic failure by reason of thrombus formation. In such cases, platelet tests may be helpful. A fall in total count may indicate thrombus formation; maintenance of count may reassure one of its absence.

The effect of anticoagulant drugs on platelet adhesiveness is quite different. As shown by Wright, Spooner and Meyer, and others, heparin and dicumarol tend to lower platelet adhesiveness. Our own studies are in agreement, a sharp drop in platelet adhesiveness being seen after heparin. Total count remains unchanged or, more often, rises, probably because of diminished lysis. Dicumarol has much less effect, even in large doses. The protective effect of heparin against thrombosis may well lie as much in its limiting effect on platelet adhesiveness and lysis as in its anticoagulant action, the common factor being inactivation of thrombin.

Thrombocytopen and Thrombocytosin. The remarkable suspension stability of platelets in the circulating blood and their equally remarkable tendency to clump and adhere under certain conditions speak for the existence of homeostatic forces of an exquisitely balanced nature. It is unlikely that plasmatic factors are wholly responsible. Differences in platelet behavior are known to exist between newly formed and older platelets and between those of different persons and species, which suggests intrinsic protoplasmic differences.

Since 1944, the writer has been interested in two chemical substances which seem to be physiological antagonists in the manner in which they influence platelet count and adhesiveness. One of these is associated with adipose tissue. A meal rich in animal fat (including egg yolk) has been shown to provoke a distinct rise in platelet adhesiveness and, to some extent, in count. The efficacy of a diet rich in such fats in relieving purpura has been known for several years. On the other hand, the proneness of obese persons to thrombosis and the increased incidence of thrombosis on a diet containing much fat have also been known for some time and have led to the use of fat-poor diets in combatting this tendency in surgical patients. Schiff

and Hirschberger (1937) postulated the existence of a hypothetical substance (Factor "T"). In 1944, the writer obtained a lipid from adipose tissue, egg yolk, lymph node, and normal spleen which caused marked thrombocytosis in rabbits. He named this lipid "thrombocytosin." Later, it was found to be capable of causing a rise in platelet count and adhesiveness and of shortening bleeding time in man. It has proved helpful in the treatment of purpura hemorrhagica.

On the basis of the above data, we have adopted a working theory according to which thrombocytosin is mobilized from tissue stores by cellular injury possibly through incidental liberation or activation of proteolytic or lipolytic enzymes, increasing thereby the tendency to thrombosis. The example of cancer of the pancreas may be cited. In this condition, which is noteworthy for frequent complication by thrombosis, circulating lipases are found in significantly increased amounts. In one case associated with mesenteric thrombosis, we have observed exceptionally active proliferation of megakaryocytes in the bone marrow. We are unable yet to offer any sound explanation for the manner in which thrombocytosin "primes" blood platelets for adhesion or accelerates their formation from their parent megakaryocytes.

Essential thrombocytopenic purpura may represent the direct antithesis of increased tendency to thrombosis (thrombophilia). Here, the prolonged bleeding time and fragile, toneless condition of the small blood vessels are associated with low platelet count and very low platelet adhesiveness. The megakaryocytes, despite normal numbers, exhibit failure of cytoplasmic segmentation into platelets. These findings are abruptly reversible by removal of the spleen. Troland and Lee (1938) and several others have reported the presence of an extractable factor in the spleen of such cases ("thrombocytopen") which can produce thrombocytopenia in rabbits and other animals.

Similar findings were obtained by the writer in 1944 in the case of a hyperplastic spleen removed from a 23-year old male patient with thrombocytopenic purpura of 6 years' duration. Within 2 weeks, his platelet count rose from 43,000 to 550,000. The possibility that thrombocytopen may be lipid in nature was suggested by the discovery of sudanophilic inclusions in the hyperplastic reticulum cells of this patient's spleen. A lipid extraction procedure was developed which proved successful in obtaining thrombocytopen also from normal spleen, although in much less quantity. The initial studies also revealed the necessity for separating an antagonistic lipid. The latter (thrombocytosin), as indicated previously, was also found in adipose tissue, lymph node, and egg yolk. Both were found in the urine.

Subsequent studies have yielded evidence that thrombocytopen and thrombocytosin have opposite effects on platelet adhesiveness *in vitro* as well as *in vivo* in rabbits and in man. In a limited study, thrombocytopen was also shown to be capable of lowering the total platelet count and platelet adhesiveness in patients having abnormally high count and adhesiveness and a clinical course marked by repeated episodes of thrombosis.

We have been led, therefore, to include in the working theory mentioned previously the proposition that the normal spleen, through its production of thrombocytopen, exerts a moderating influence on the tendency to thrombosis by limiting the number and adhesiveness of blood platelets. It is possible that splenic function is adjusted to fluctuating physiologic needs by homeostatic mechanisms, as in the case of other endocrine glands.

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SECTION OF PSYCHOLOGY

SOME CONTRIBUTIONS IN SUPPORT OF A NEUTRAL THEORY OF PERSONALITY*

By THOMAS N. JENKINS†

The present study is based on an analytical approach to the investigation of personality organization, that is, the treatment of personality as if it comprised a large number of variates, often referred to as traits. The point of view to be discussed here involves two fundamental theorems. According to our first theorem, *personality trait factors contain variances which comprise two independent basic factors or superfactors*. Contrary to what one might surmise, these superfactors are neither antagonistic, oppositional, reciprocal, nor bipolar. In fact, our evidence indicates that they are statistically independent behavior tendencies, and hence neutral to each other.

The second theorem asserts that *personality factors are unipolar*, and, by implication, constitutes a general denial of bipolar factors of personality. This theorem is not necessary for the truth of the first one, but it is important for its rationale as a part of a general theory of personality. Cyril Burt[1–3] is largely responsible for emphasizing and directing attention to the concept of bipolarity in modern factor theory. The notion of bipolar factors, however, is not new. The bipolar concept is not only recognized in current personality theories, but is implied in modern personality tests. In fact, some tests, such as the ascendance-submission test of Allport, have been given bipolar trait names. Other test-makers, as for example, Bernreuter and Guilford, describe their scales in bipolar terms. It is assumed, for instance, that depression and its semantic opposite, are at opposite ends of a common scale. The Guilford-Martin Profile Chart describes the depression scale as follows: "A high C- score indicates freedom from depression, a cheerful, optimistic disposition. A low C- score indicates a chronically depressed mood including feelings of unworthiness and guilt." In discussing the Guilford-Zimmerman Temperament Survey, the test-makers speak of dimensions with opposite poles and describe their test scales in terms of negative and positive qualities.[4]

If personality traits tend to be unipolar instead of bipolar, then the scores on tests such as those just mentioned are likely to be mixed scores instead of values along a single trait axis or continuum. For instance, let us assume that depression and buoyancy (tendency to be elated) are uncorrelated traits or behavior tendencies. Then a test scale containing both depression and buoyancy items would result in a rather meaningless or ambiguous composite score for the two traits. This possibility may account for some of the difficulties in using current personality tests effectively in clinical work, and in the selection and allocation of industrial and military personnel.

It is worthy of note, in this connection, that Thurstone and his co-workers, although furnishing no positive evidence against the existence of bipolar personality factors, have failed to discover any bipolar factors. Recently, Thurstone[5] factor-analyzed the thirteen scores of the Guilford series to determine the number of dimensions in these personality schedules. "We started this analysis," he states, "with the expectation of finding bipolar factors for all or

* This paper was presented at the meeting of the Section on October 16, 1950.

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most of these factors, but the result revealed all of them to be positive."

The present theory is the outcome of an extensive exploratory survey of personality, involving both laboratory and test studies. By laboratory work, we refer to records of such behavior as sweating, sway, autokinesis, cutaneous reactions to temperature changes, postural behavior, circulatory changes during kinesthetic and neural mobilization, muscular tension, tremor, EEG, and perceptual and attitudinal behavior under various background conditions. The data for discussion here, however, are based primarily on human behavior in test situations.

Experimental test batteries involving different types of self-appraisal response scales were tried out on several thousand subjects. These scales involved appraisals in terms of trait loading (how much?), frequency (how often?), and attitudes. The face validity of the items varied from high to little or no face validity. An example of a low face validity item would be the following: "I like to watch water gushing from a fountain."

In analyzing the responses to these batteries of items, the factorial approach was utilized throughout. The frequency response study is nearly finished and has resulted in a test of over 100 personality trait scales. An analysis of these test scores yields information in support of the two theorems previously referred to. Scoring categories, which seem to be semantically opposite or antonymous, proved to be statistically independent. In other words, scoring categories which are semantically opposite seem to be measures of traits which are organically or functionally independent.

Some examples of such relationships are presented in TABLE 1. Here, it will be noted that buoyancy and depression are practically uncorrelated ($r = -.07$). Similarly, a low negative correlation exists for dynamism and lethargy. Dynamism is defined as the tendency to feel lively or energetic; lethargy, as the tendency to feel unenergetic, drowsy, or tired. *Such results may seem confusing, if we fail to keep in mind the fact that behavioral tendencies rather than behavioral effects are uncorrelated.* For example, possessing both buoyancy and depression to a high degree does not mean that an individual must be happy and depressed at the same time.

TABLE 1
EXAMPLES OF RELATIONSHIPS BETWEEN TEST SCORES WHICH ARE SEMANTICALLY OPPOSITE YET UNIPOLAR*

Test	Group I				Group II				
	1	2	3	4	5	6	7	8	9
I. 1. Buoyancy									
2. Dynamism	55								
3. Emotional spontaneity	54	56							
4. Carefreeness	45	57	32						
II. 5. Depression	−07	−27	−29	−15					
6. Lethargy	00	−22	−13	−21	59				
7. Hypersensitiveness	20	−03	02	−15	54	43			
8. Anxiety	−03	14	−23	−24	50	46	57		
9. Feeling of social insecurity	−13	−11	−22	02	53	42	66	63	

* Group I is significantly loaded with *C* variance, Group II with *A* variance.

The correlation coefficients in TABLE 1 are arranged into two groups, corresponding to two superfactors, hereinafter referred to as factors *C* and *A*. It will be noted that the scores in group I correlate significantly and positively with each other, but correlate low with the scores in group II. Group I is loaded with factor *C* and group II with factor *A*. Some insight into the

nature of these superfactors may be gleaned from the scores which are most heavily loaded with them. Buoyancy, dynamism, spontaneity, and carefreeness, for instance, are significantly loaded with *C*, while depression, lethargy, hypersensitiveness, anxiety, and feelings of social insecurity are variously loaded with the *A* factor. The correlation of these test scores and others with laboratory data recorded by George Retholtz suggests that sway, palmar sweating, and autokinesis are associated with *C*, while circulatory changes during stress are more closely related to *A*.

The next step in our investigation will be an attempt to develop test scales for these two superfactors. It might be added that we have already studied the effect of test reticence on the intercorrelations between the test scores. Partialing out test reticence tends to reduce the within-group correlations but also reduces the negative between-group correlations, so that the over-all pattern of relationships remains the same.

Probably, a note of warning should be issued at this time concerning the use of these superfactors in appraising personality. Though these factors seem to be common to a large number of trait scores, they constitute only a part of the total factor variance of these scores. Other portions of the total variance, that is, those corresponding to specific traits, can be very important for interpretation. For example, two subjects, whom we will refer to as H and K, were both heavily loaded with *C* and lightly loaded with *A*. On this basis, H and K would seem to be very similar. H received a low submissive score (15 percentile), however, while K received a high submissive score (95 percentile). Both men were successful salesmen, but their conduct in handling their environments was very different. What would happen if a person were high on both *C* and *A*? Here again, probably, much would depend on the trait pattern of the individual. One subject, high on both factors, was variously described by his supervisors as "ambitious," "a postponer," "tends to ride in all directions at once," "gets lost in a maze of details," "seems to become befuddled," "sometimes functions well while at other times he seems confused and unable to act."

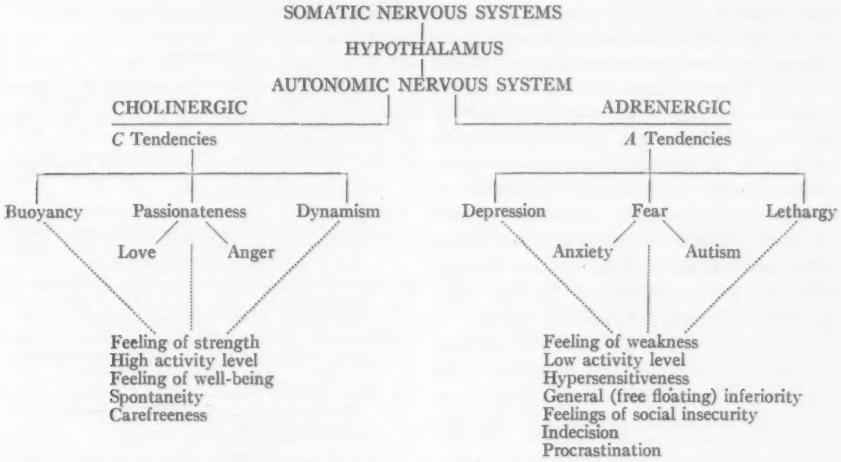

FIGURE 1. Suggested relationships between the neural basis of *A* and *C*, and traits closely associated with these superfactors.

Before closing this paper, I would like to suggest a physical basis for the *C* and *A* superfactors. Recent studies suggest that anxiety, chronic fatigue, and depressed activity are associated with the sympathetic component of the autonomic nervous system. Considerable confusion seems to have arisen, however, because of a rigid adherence to anatomical origins. Darrow[6] was one of the first investigators to show that behavior which is parasympathetic in character may be mediated through postganglionic sympathetic fibers. He noted that stimuli producing marked changes in palmar resistance induced very little change in blood pressure, while situations eliciting large changes in blood pressure resulted in very little change in palmar resistance. The sweat glands are innervated by sympathetic nerves, but activated through the release of acetylcholine. Acetylcholine, however, is usually released by postganglionic parasympathetic fibers, while adrenin-like substances are usually, but not always, produced by the postganglionic sympathetic fibers. Dale,[7] in 1933, suggested that activation of effectors by means of acetylcholine should be called cholinergic, regardless of the anatomical origin of the neural conductor. He suggested the term, "adrenergic," for activation by adrenin-like chemicals, such as sympathin.

It may be that the *C* superfactor is associated with cholinergic activity and the *A* superfactor with adrenergic activity. A suggested schema of relationships between *A* and *C* behavior tendencies and the nervous system is outlined in FIGURE 1. Among the cholinergic or *C* behavior tendencies would be buoyancy, dynamism, and passionateness, while the adrenergic group would comprise such tendencies as depression, fear, and lethargy.

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SECTION OF MATHEMATICS AND ENGINEERING

HEATING OF FLUIDS IN COILS*

By RALPH R. BERG† AND CHARLES F. BONILLA‡

Commercial heat exchangers are, almost without exception, constructed of straight tubes fastened rigidly to two "tube sheets" and surrounded by an outer "shell." One fluid flows within the tubes and the other outside of the tubes and within the shell. This arrangement has the advantage of easy cleaning of the inside of the tubes, solidity, and convenience for large flow rates. Thermal stresses may be large, however, due to the rigidity of the construction, and, to obtain high fluid velocity, long flow path, and high heat transfer effectiveness, complicated headers are necessary in order to obtain a number of flow paths in series.

The use of single or multiple helical coils in place of the straight tubes has some

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disadvantages, such as difficulty of internal cleaning, but it avoids the previously mentioned drawbacks of straight tubes and usually even eliminates the need for tube sheets. In addition, it might be anticipated, particularly in viscous flow, that the heat transfer coefficient would be considerably higher than with straight tubes because of the velocity distribution obtained. The higher momentum of the stream at the center causes a double corkscrew form of convection in the coil, the central core continually pushing radially outward, then slowing up due to friction and moving around both sides circumferentially toward the inner surface of the coil as it advances. This continual motion of the central portion of the stream past the walls would be expected to decrease the thermal resistance considerably in viscous flow from the tube walls to the bulk of the stream, as the similar motion caused by natural thermal convection is known to do in horizontal straight tubes.[2]

No heat transfer experiments have been reported on viscous flow in coils, however, and in turbulent flow only the overall coefficient from water to water found by Richter[5] and the film coefficients to air obtained by Jeschke[4] are available. Evidently, a more comprehensive study of heat transfer in coils, particularly in viscous flow, was necessary before even approximate design of heat exchangers with coils would be possible.

Apparatus. Number 16 B.W.G. soft copper tubing filled with rosin or low melting metal was wound into three coils on a rotating mandrel in a lathe. The dimensions were as follows:

Designation of coil	*Large*	*Small*	*Intermediate*
Nominal tubing I.D. (in)	3/4	1/4	1/4
Exact average tubing I.D. (in)	0.744	0.283	0.236
Nominal coil C.L. diam. (in)	4.5	1.5	4.5
Exact average coil C.L. diam. (in)	4.52	1.50	4.07
Diameter ratio, D_H/D	6.08	5.30	17.21
C.L. pitch (in)	1.75	0.75	0.75
Coil length (ft)	25.	6.	20.

Measurements of the radial and axial outside diameters after bending showed that the large coil had been radially flattened about 6.5 per cent and the others about 2.3 per cent. The inside wall of the large coil was smoothly corrugated to the extent of several per cent of the diameter, with a wavelength of about one tube diameter. It was not felt, however, that this affected the results appreciably. Two pressure taps and eight thermocouples were carefully installed on the outside of each coil. The thermocouples were made of constantan wire inserted in 0.03 inches O.D. copper tubing, soldered into slots at representative positions in the tubing and filed until flush. Outer heating jackets from 6 to 24 inches long were employed around the coils, with a rubber diaphragm in each end perforated to receive the tubing snugly, as well as the tubular thermocouples. Accurate thermometers in fluid mixers gave the inlet and outlet fluid temperatures.

Operation and Results. Air and water passed through the coil once, but oil was continually recirculated through the coil and a cooler. The shell was heated by means of atmospheric pressure steam in excess. To obtain film coefficients directly, the wall temperatures were measured. All tests were run until steady state was reached.

A total of 120 heat transfer runs was carried out with the three coils and three fluids. The method of analysis of the runs required plotting the tube wall temperatures against axial length and drawing in a smooth curve. The total distance between the end diaphragms was divided into equal sevenths, and, starting with the fluid inlet temperature, the fluid temperature was computed successively at each of the seven positions, with an assumed constant value of heat transfer coefficient, h, and the arithmetic mean temperature difference over the interval. If, after the seventh interval, an exact check with the recorded

fluid outlet temperature was obtained, the correct average, h, had been assumed. If not, the procedure was repeated, with a new value of h, until an exact check was obtained on the outlet temperature or enough trial results were obtained to interpolate to the correct average h.

Physical Properties of the Fluids. The physical properties required to correlate the results are all known accurately for water and air. For the oil, however, obtained from a single drum of Essolube 30, it was felt desirable to measure the density, viscosity, and thermal conductivity. The first was measured in a picnometer and the results can be expressed by the equation:

$$\rho = 58.39 - 0.01102\ t \qquad (1)$$

for ρ in lbs./cu. ft. and t in °F. The viscosity was measured in a calibrated Saybolt viscosimeter, the following values being obtained:

t, °C	48.7	67.7	87.5
μ, poises	0.5670	0.2498	0.1292

Interpolation was carried out by a straight line ASTM viscosity—temperature chart. The thermal conductivity was determined by comparison with glycerine in a double chamber cell of the type employed by Dittman and Winding.[3] All precautions were taken, including heating the liquids before tests to eliminate dissolved gas, testing with the oil and glycerine in reversed positions, and computing the thermal conductivity of the oil from the separate relative conductances in both positions on the assumption of unequal thicknesses of the two chambers. In addition, measurements were made at 5°, 10°, 20°, and 30°C. overall temperature difference for chamber thicknesses of 1 in. and $\frac{1}{4}$ in.

To eliminate the effect of natural convection, the computed value of thermal conductivity for each thickness was extrapolated to zero temperature difference, and for each temperature difference, to zero thickness. The results were not entirely consistent but were definitely lower than the values reported by the Esso Blue Book. It was decided to adopt the same slope of k *vs.* temperature as shown by their three points, but with values $1\frac{1}{2}$ per cent lower, which is expressable by the equation:

$$k = 0.0800 - 0.00002464\ t \qquad (2)$$

for k in BTU/hr. ft. °F. and t in °F. for 0° to 220° F.

The specific heat was computed by the usual formula (1) and for this oil can be expressed as:

$$c = 0.403 + 0.0004688\ t \qquad (3)$$

for t in °F.

Comparison of Heat Transfer Results with Previous Literature

In streamline flow in straight tubes, heat must be transferred by conduction over the total radius of the tube. In turbulent flow, however, convection of fluid occurs and the thermal resistance is mainly that of a relatively thin and constant "boundary layer" in streamline flow against the wall. Accordingly, the heat transfer coefficient is generally independent of tube length in turbulent flow but decreases downstream along the tube in streamline flow as the average distance the heat travels by conduction increases. Due to the convection of the fluid between the center of the tube and the walls that occurs in streamline flow in coils, the heat transfer coefficient would be expected to approach independence of tube length. Another case which is qualitatively similar is that of thermal natural convection in a straight horizontal pipe in streamline flow. In both of these cases, particularly if the double corkscrew convection is strong, the local and therefore the average heat transfer coefficient would not involve tube length in their correlations. Furthermore, they should be computed from the area-averaged temperature driving force, as in turbulent flow, rather than from the arithmetic mean driving force, as in straight-line streamline flow.

Turbulent Flow Correlation. First, a standard turbulent flow correlation was tested. The form employed was a plot of (Nusselt number) $\times$ (Prandtl number)$^{-0.4}$ *vs.* (Reynolds number), using average bulk

temperatures for the physical properties. The turbulent flow runs with water were seen to agree fairly well with the equation for straight pipe, but the streamline flow points were lower for air and higher for oil. Evidently, no general correlation for the streamline region was obtained on this basis. However, the intermediate or least tightly wound coil, in all cases, yielded coefficients than the others with air, but higher with oil. The qualitative observation may be made that most of the points lie well above the straight pipe values. It is difficult, in fact, to understand how any of them can be below it, as quite a few actually are.

Natural Convection Correlation. Heat transfer by thermal natural convection to

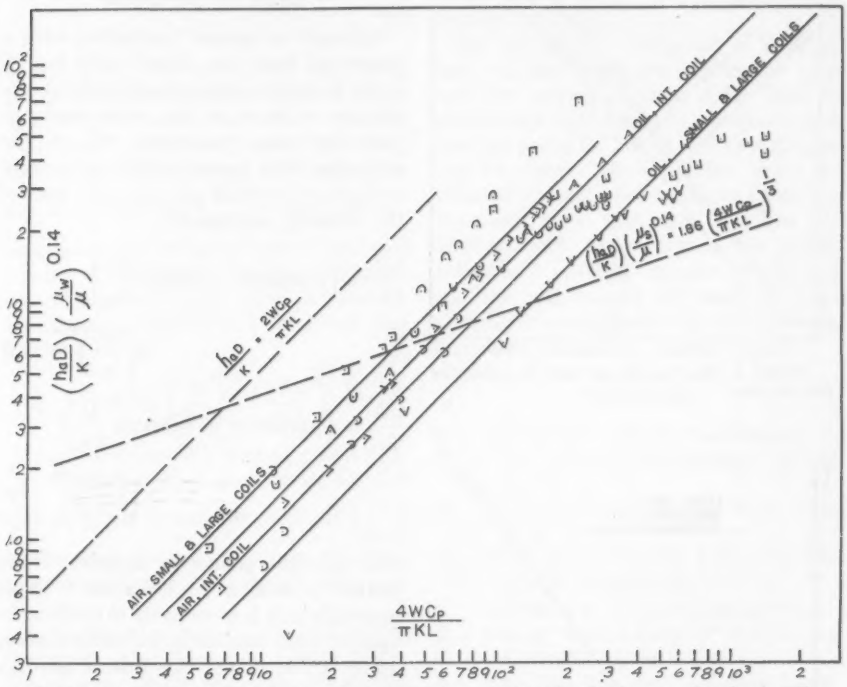

FIGURE 1. Streamline flow mechanism in straight tubes applied to heating in streamline flow in coils.

coefficients about half those of the other two coils.

Streamline Flow Correlation. The usual plot for streamline flow in straight tubes, employing $h_{a.m.}$, based on overall arithmetic mean driving force with a constant wall temperature, is shown in FIGURE 1. Again, no general correlation for flow in coils seems possible, as might have been expected from the previous discussion. In fact, here the intermediate coil gives lower

stationary fluid inside a horizontal tube could be correlated, as it is outside, by a function of the Nusselt, Grashoff, and Prandtl numbers. The Grashoff number is defined $\left(\frac{D^3\rho^2 g\beta\Delta t}{\mu_f^2}\right)$, in which the maximum differential force per unit volume of fluid due to the thermal expansion is represented by the product $(\rho g\beta\Delta t)$. Since the centrifugal force in flow in a coil could be considered comparable, it is logical to try replacing

$(\rho g\beta\Delta t)$ with $(2\rho V^2/D_H)$. All the runs were plotted in this way, but again, no worthwhile correlation was obtained, since the points spread by a power of 10 in Nusselt Number. In addition, the intermediate coil was lower than the other two coils with air, higher with water, and in between with oil. Although the average slope and location were fairly close to those for thermal natural convection outside a pipe, it did not seem worth while to work on this correlation any further.

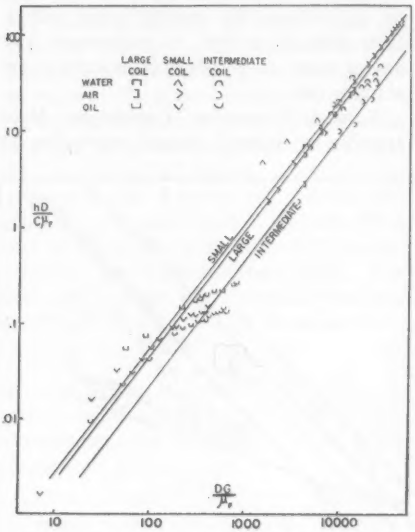

FIGURE 2. Heat transfer to fluids in streamline flow in coils.

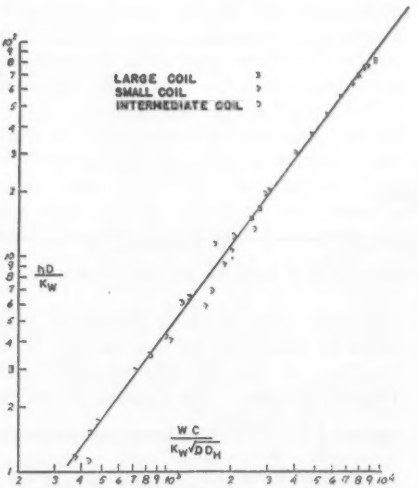

FIGURE 3. Heat transfer to air in streamline flow in coils.

Empirical Correlations

Although no general correlation with a theoretical basis was found valid for all of the fluids and coils, several empirical correlations of more or less widespread applicability were uncovered. All of the streamline data agreed within an average deviation of some 20 per cent with each of the following expressions:

$$\frac{hD}{C\mu} = \left(0.0000355 + 0.0009\,\frac{D}{D_H}\right) \cdot \left(\frac{DG}{\mu}\right)^{1.26} \quad (4)$$

$$\frac{hD}{C\mu_f} = \left(0.0000229 + 0.000636\,\frac{D}{D_H}\right) \cdot \left(\frac{DG}{\mu_f}\right)^{1.29} \quad (5)$$

The principal groups in equation 5 are plotted in FIGURE 2. Equation 5 seems preferable as it is more likely to continue to hold for other conditions, including cooling, which is due to the fact that it employs viscosity at the average film temperature. It is to be noticed, however that thermal conductivity is not present in these correlations. They should be used with caution until verified further.

A correlation for the heating of air in streamline flow was obtained that had an average deviation of less than 10 per cent. It is shown in FIGURE 3. The equation for the line is:

$$\frac{hD}{k_w} = 0.000468\left(\frac{WC}{k_w\sqrt{DD_H}}\right)^{1.33}. \quad (6)$$

Equation 6 can be rewritten as:

$$\frac{hD}{k_w} = 0.00034\left(\frac{D}{D_H}\right)^{2/3}\left(\frac{GDC}{k_w}\right)^{1.33} \quad (7)$$

for readier comparsion with Jeschke's equation[4] for air in turbulent flow:

$$\frac{hD}{k_w} = \left(0.039 + 0.138\left(\frac{D}{D_H}\right)\right) \cdot \left(\frac{GDC}{k}\right)^{0.76}. \quad (8)$$

It is seen that the influence of velocity on the heat transfer coefficient is less in turbulent flow, as would have been expected. Equations 7 and 8 seem not to be entirely consistent, however, since, on solving them simultaneously with $\left(\frac{C\mu}{k}\right) = 0.68$, the unreasonably high values of critical Reynolds number of 110,000 and 244,000 are obtained for coil to tube diameter ratios of 6 and 18, respectively. Equations 6 or 7 can also be rewritten as:

$$\frac{h}{CG} = 0.00034\left(\frac{D}{D_H}\right)^{2/3}\left(\frac{GDC}{k_w}\right)^{0.33} \quad (9)$$

It seems quite possible that equations 6, 7, and 9 hold for other gases beside air, but they could not be valid for values of $\left(\frac{D}{D_H}\right)$ smaller than that at which they equa lthe h predicted by standard straight pipe correlations.

A correlation similar to FIGURE 3 for the heating of water showed an average deviation of some 20 per cent from the experimental points. Though this is probably no more reliable than equation 4 or 5, it is much simpler and should be suitable for approximate design over the ranges covered. The equation of the best straight line can be rewritten in the following form, which is comparable to that of equation 9:

$$\frac{h}{CG} = 0.524\left(\frac{D}{D_H}\right)^{\frac{1}{3}} \quad (10)$$

A plot for oil similar to that of FIGURE 3 gives still larger deviations, and equation 4 or 5 would be preferable for other fluids than air and water.

Summary

A streamline flow of air, water, and SAE 30 lubricating oil was produced in each of three coils, $1\frac{1}{2}$ and $4\frac{1}{2}$ inches in centerline diameter, made from $\frac{1}{4}$ and $\frac{3}{4}$ inch I.D. tubing and surrounded by a steam jacket. With water, turbulent flow was also produced.

An approximate correlation of the film heat transfer coefficient inside the pipe valid for heating all three of the fluids in viscous flow was found, and a more accurate one was found for air, as well as a simpler one for water. Heat transfer is not facilitated by coiling the tubing to the extent that had been anticipated for the oil, however, and, particularly at the higher velocities, the heat transfer coefficients and the heat transfer efficiency are considerably improved, with respect to pressure drop, over those with straight pipe.

Nomenclature

- C specific heat of the fluid flowing, at its average temperature (BTU/lb. °F.).
- D average internal diameter of the tube (ft.).
- D_H diameter of the helix formed by the axis of the tube (ft.).
- g acceleration of gravity (ft./hr.^{2}).
- G average mass velocity of fluid in the tube, (lbs./ft.^{2} hr.).
- h film heat transfer coefficient based on true average Δ t (BTU/hr. ft.^{2} °F.).
- h_a film heat transfer coefficient based on arithmetic mean Δ t (BTU/hr. ft.^{2} °F.).
- j heat transfer factor, $\left(\frac{h}{CG}\right)\left(\frac{C\mu}{k}\right)^{2/3}$ (dimensionless).
- k thermal conductivity of the fluid at its average temperature (BTU/hr. ft. °F.).
- t temperature (°F.).

Δt average temperature difference from the tube wall to the fluid (°F.).
V average linear velocity of the fluid in the tube (ft./hr.).
W total flow rate of the fluid (lbs./hr.).
α "average" angular acceleration ($2V^2/D_H$) (ft./hr.^{2}).
β average volumetric coefficient of thermal expansion of the fluid (1/°F.).
μ average absolute viscosity of the fluid (lbs./ft. hr.).
ρ average density of the fluid (lbs./ft.^{3}).

Subscript

f at average film temperature (average of fluid and tube wall average temperatures).
H for the helix or coil.
S for straight pipe.
W at the average tube wall temperature.

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SECTION OF ANTHROPOLOGY

EARLY MAN ON THE BERING SEA COAST*

By J. L. GIDDINGS, JR.†

Nineteenth century theories about the peopling of the Americas often centered about the narrow sea channel between Alaska and Siberia, as do current balances of opinion, but, in spite of this, we are only now beginning to turn up, on the shores of the Bering Strait gateway itself, the sorts of stone tools that early migrants might be expected to have left behind.

Although the possibility is by no means exhausted, the finding in this area of either a paleanthropic skeleton (such as Peking Man or Neanderthal) or the hand-axe and chopper sort of cultural context that goes with the middle of the glacial age in Europe and Asia would come as a surprise to most archaeologists. On the other hand, there is hardly a technique or specialism in stone that belongs to the last phases of the Paleolithic period of Europe, the Mesolithic, or the Neolithic and not also to some cultural horizon of the New World. This is not to say that each form of a flint time-marker for these periods in Europe can be duplicated in America. It is to say, rather, that Americans have not lacked the basic techniques that would have enabled them to duplicate Old World forms had they so desired. We should therefore expect to find in Alaska stone objects formed by the same basic techniques as those of the earliest known American cultures, provided these techniques were also known on the Eurasian continent.

An association of flint artifacts that appears to fulfill this basic requirement, thus placing itself in the position of either a parent New World culture or the relict of one, has recently been described from a coastal site in Alaska at the neck of Seward Peninsula and seems to be represented in two more recent finds northward of this point. This association, known as the Denbigh Flint Complex, was discovered in 1948* underlying Eskimo cultural de-

* This paper, illustrated with Kodachrome slides, was presented at the meeting of the Section on October 23, 1950.

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* GIDDINGS, J. L., Jr. Early Flint Horizons on the North Bering Sea Coast. J. Wash. Acad. Sci. **39:** 85–90. 1949.

posits on a 40-foot terrace at Cape Denbigh overlooking Norton Bay, the most northwesterly extension of Bering Sea. A second season of excavation at the site revealed the stratigraphic separation of the oldest cultural deposits from the later ones and uncovered some 900 artifacts of the Denbigh Flint Complex in place. During the same summer season of 1949, Dr. Helge Larsen explored a series of limestone caves in the mountains of the north side of Seward Peninsula, bringing forth from the lowest levels of one cave certain objects that seemed out of the range of the known Eskimo cultures but compatible with the Norton Bay finds.

The intriguing nature of these separate discoveries led to the organization of the Bering Straits Expedition of 1950. Froelich Rainey, Helge Larsen, and the author, representing respectively the University of Pennsylvania Museum, the Danish National Museum, and the University of Alaska, and supported by a generous grant from the Viking Fund, planned a coordinated attack on problems of cultural sequences in the area between Bering Strait and the neck of Seward Peninsula. Aided by eight students and research assistants and several Eskimo workmen, we were able to draw together the threads of our jointly considered research of the decade following our first field association, at Point Hope in 1939, to a focus on Seward Peninsula.

Dr. Rainey explored the coast between Cape Prince of Wales and Nome, Dr. Larsen returned to the Trail Creek Caves, and my group continued at Cape Denbigh. Since the full results of the 1950 season concern archaeological sites of several places and periods, a full integration of which cannot now be made, we shall pass briefly over all but the earliest cultural horizons at Cape Denbigh.

The site at Cape Denbigh, as we knew at the beginning of the third season of excavation there, is one of those rare sites of the Arctic area in which the remains of one culture are superimposed on those of another. Three such cultures, not to mention possible sub-phases, are distinguished there by both cultural content and hiatuses marked by vegetation and soil changes. A vertical section through a part of the site where neither the digging of pits for sub-surface structures nor erosion has altered the gradual accumulation of soil and cultural debris reveals a sequence somewhat as follows:

Beginning with the surface, one finds a thick layer of sod and bunch grass, the matted roots of which contain little cultural matter. Directly below this carpet of vegetation lie the thick potsherds, polished slate, and other objects of what we choose to call the Neo-Eskimo.* If we may judge from comparative typology with other North Alaska sites, this occupation lasted for several centuries, terminating locally some 300 years ago. Below this level, and separated in some parts of the site by a sod layer, lies a bed of fine-grained loam, containing the stone lamps and flaked stone tools of basalt that bear the stamp of the earliest known Eskimo cultures elsewhere. This may be designated the Palae-Eskimo zone. Under the lowest leavings of this Palae-Eskimo deposit is a rather thick deposit of sandy silt loam, which contains no cultural leavings whatever. The Denbigh Flint Complex occurs in place only at the base of this sterile deposit, in a normally pencil-thin coating of the clay that tops and consolidates a disintegrated bedrock.

The Cultural Position of the Denbigh Flint Complex. We wonder if the Denbigh Flint Complex represents a base out of which Palae-Eskimo manifestations grew. The possible links between the two sorts of culture appear highly tenuous. While it is true that a form of lenticular side blade has the same outline in the two cultures, it is also apparent that those side blades of the Denbigh Flint Complex are mainly, if not wholly, manufactured from lamellar flakes. The technique of preparing cores

* Following the broad divisions proposed by Helge Larsen and Froelich Rainey in "Ipiutak and the Arctic Whale Hunting Culture" (Anthropological Papers, American Museum of Natural History, 1948).

and striking lamellar flakes is lacking in the known coastal sites of the Palae-Eskimo. Similarly, the forms of certain flake knives, or side scrapers, and of possible harpoon blades, conform in both horizons, while the techniques of preparation differ.

Aside from these points of resemblance, the objects recovered from the lowest level at Cape Denbigh bear little or no similarity to objects assignable to a Western Eskimo origin. They do, on the other hand, identify themselves largely with forms and techniques of either the Old World Paleolithic and later cultures or the Folsom and Yuma horizons of the southwestern United States. Into the former category fall several varieties of true burin (gravers in the British sense), snail-like keeled scrapers, retouched points or blades made of lamellar flakes, broad plano-convex points, and a saw of flint. Relation to early American flints is shown in large, diagonally-spalled blades, fluted points, the "Folsom graver," and certain side scrapers.*

The microlithic nature of the complex is also to be considered. Aside from the few examples of large points such as may have capped spears, all of these objects are markedly delicate and small. The finest of the miniature, diagonally-flaked blades made of lamellar flakes represent the most meticulous work in flint of which we have knowledge. One thin blade only three centimeters long has more than 20 parallel, diagonal scars on each face. Among the 1500 or more worked objects thus far recovered in place, there is not one large stone tool such as an adze, hammer, grinding slab, or grooved stone. In the absence of organic materials, little can be conjectured about those tools that must have been required for working large and heavy substances such as driftwood logs.

The Denbigh Flint Complex is unique in its total assemblage, although we can point to striking similarities between groups of its objects taken out of context and similar selections from widely separated early sites on the continents on either side of the Bering Strait.

Some idea of the areal distributions of the Denbigh Flint Complex is gained from the presence of small blades of the Denbigh type in lower levels of the Trail Creek Caves, some 100 miles to the north, and from the discovery by Wm. Irving of the University of Alaska, in 1950, of burins and microliths in an eroding sand dune area in Anaktuvuk Pass of the interior of north west Alaska. A full description of these sites by Dr. Larsen and Mr. Irving will help to place the Norton Bay finds in a frame of other Early Man finds in Alaska.

Indications of the Time Involved. Speculation upon the age of the Denbigh Flint Complex combines cultural-stratigraphic evidence with that of geological change. The position of Palae- and Neo-Eskimo levels well above the stratum in question affords a relative time scale for the local area, although we know little of the actual beginnings of either of the Eskimo manifestations elsewhere.

Geologically, the Denbigh Flint Complex layer offers exceptionally clear-cut evidence of considerable age. The terrace upon which the deposit lies consists of a matrix of angular boulders of local limestone and the clayey substance into which they dissolve. No evidence of human occupation has been found within this base. The earliest people to camp at the site, however, left their flints in such a position that they are now concentrated on the surface of the thin layer of clay coating the "bedrock" matrix. The absence of any sign of digging into this clay or of trampling the flints into it indicates that, at the time of occupation, the people concerned walked on some sort of surface carpet of vegetation which has since disappeared. Above the culture layer on the clay rests as much as seven feet of sandy silt and silt loam, the lower region of which is sterile.

The first two seasons of excavation dealt with the deeper parts of the site. Although more than 400 square feet of the oldest level in place were exposed, only one possible

* These relationships are elaborated by the author in a forthcoming paper, "The Denbigh Flint Complex." American Antiquity 16 (3). January, 1951.

hearth area came into consideration. This was at the highest point of investigation, at the edge of a slope where the terrace joins the hillside. Excavations of 1950 concentrated on this area. In a series of parallel rectangular pits, we exposed the top of clay and its coat of cultural material over a wide area, finding five more hearths. A series of folds occurred here in which flints of the dark culture layer remained on the top of clay even where the folds had as much as two feet of overlap. These folds had not affected the stratification above, and hence must be referred to a period before those deposits had accumulated.

We were fortunate in having a geologist visit the site at this stage of discovery. David M. Hopkins, of the Terrain and Permafrost Section of the United States Geological Survey, spent three days examining the site and the local geology. Although a written report has not yet been received from Dr. Hopkins, we may anticipate some of his findings.

First of all, the northwest side of Cape Denbigh is not now permanently frozen, nor does it seem to have been an area of permafrost in recent times. At present, ice penetrates the ground from the surface each winter, then retreats the following summer. At the time when the folding of the bottom clay layer at the site occurred, however, frost lay deep beneath the surface. The folds themselves form a "solifluction lobe" about forty feet across. Such lobes are common phenomena of permafrost areas in north Alaska at the present time, resulting from the thawing of a fine-grained soil below an elastic ground cover and above frozen ground. The confined, water-laden soil moves by gravity down the slope in folds, although it is unable to break its sod cover.

The Denbigh Flint Complex was thus already deposited at a time when solifluction lobes were forming in a climate *markedly colder* than that of the present in the Norton Bay area.

A second solifluction lobe was partly exposed in another part of the site, where the overlying silt and loam was seven feet thick and where a layer of peat, or compacted sod, formed a continuity above the sterile zone of silty soil and the soils containing the Eskimo cultural deposits. Thus, pending receipt of Dr. Hopkins's interpretation, we seem to have evidence of a cold, a warmer, and a second cool period of climate before the relatively stable climatic conditions under which the Eskimo cultures appear.

In summary, the Denbigh Flint Complex appears to represent an old-fashioned culture recalling the earliest North American phases, as well as the pre-Neolithic Old World phases, and to have been deposited during a period of climate more like that of the glacial age than of the present. Until we are further apprised of the status of Alaskan climatic periods with respect to the rest of the world, however, we can only say that the age of the Denbigh Flint Complex almost surely must be reckoned in millenia and must be, for the present, relegated to that "floating" category of cultural remains attributed to "Early Man."

NEWS ITEMS:

Doctor Selman A. Waksman, Rutgers University, has been named to receive the 1950 Charles Mickle Fellowship by the faculty of medicine of the University of Toronto. Doctor Waksman is the thirtieth winner of the award, whose past winners include Doctor Harvey Cushing, neurological surgeon, and Doctor Charles H. Best, codiscoverer of insulin.

Doctor Orville F. Denstedt, professor of biochemistry at McGill University, was recently appointed a Co-director of Professional Affairs of The Chemical Institute of Canada, which is the national association of chemists and chemical engineers. Doctor Denstedt is also chairman of the Canadian High Polymer Forum for 1950–51. The Forum is jointly sponsored by The Chemical Institute of Canada and the National Research Council.

DIVISION OF MYCOLOGY

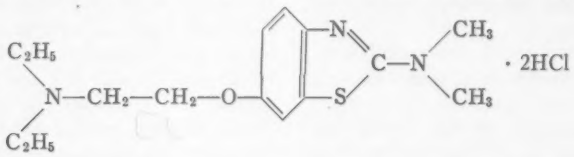
MYCOLOGICAL STUDIES WITH A NEW BENZOTHIAZOLE WITH SPECIFIC ACTIVITY AGAINST DERMATOPHYTES*

By E. GRUNBERG, G. SOO-HOO, E. TITSWORTH, D. RESSETAR, AND R. J. SCHNITZER†

Since the first description of the antifungal activity of benzothiazoles in 1932,[1] confirmatory evidence of their activity has been published by numerous investigators. The majority of these publications deal with 2-hydroxy-, 2-amino-, and 2-mercapto-benzothiazoles. The latter compound and its derivatives were most frequently found to possess quite satisfactory activity against fungi. The greater part of the work was concerned with apathogenic molds of technical importance in the field of agriculture[2–6] or of rubber or leather preservation.[7, 8] R. L. Mayer[9] included in his studies the dermatophytes and described the appreciable activity of 2-mercapto-benzothiazole against *Microsporon* and *Trichophyton*.

At sporadic intervals during the last ten years, the antifungal properties of benzothiazoles have been studied in our laboratories. The results of this work can be summarized by stating that a moderate antifungal effect towards dermatophytes is usually observed in this group of compounds.

Compounds which showed higher and more promising activity were only encountered after certain derivatives of substituted 2-amino-benzothiazoles became available through the efforts of Dr. N. Steiger and Mr. O. Keller of the Roche Chemical Research Laboratories. Approximately eighty derivatives were studied biologically during recent years. One compound, 2 - dimethylamino - 6 - (β - diethylamino-ethoxy)- benzothiazole dihydrochloride (formula 1), Asterol Dihydrochloride,* was selected for more intensive study because of its surprisingly high fungistatic effect.



(1)

Asterol is a basic ether of 2-dimethylaminobenzothiazole. The dihydrochloride is a white crystalline substance which is soluble in water and alcohol. A 5 per cent solution has a pH of approximately 2.0. Acute toxicity tests in mice gave a value of the LD_{50} of 0.375 gm./kg. by the subcutaneous route and of 0.5 gm./kg. by oral administration.

The experiments to be described in this paper were carried out with the dihydrochloride, but it should be mentioned that the base had the same antifungal properties. It is not within the scope of this presentation to discuss the possible relations between chemical constitution and antifungal activity. We should like, however, to demonstrate in TABLES 1 and 2 why we eventually selected the compound which is now called Asterol.

A commonly used fungistatic method was employed in the experiments to which these tables refer. Graded concentrations of solutions of the hydrochlorides of the compounds were incorporated into Sabouraud's agar plates. The center of the plates was subsequently inoculated with a small piece of a fungus mat from cultures of *Trichophyton mentagrophytes* or *Microsporon lanosum* and observed for eighteen

* On October 27, 1950, the Division of Mycology held a symposium on "Studies With a New Benzothiazole Derivative." This paper, illustrated with lantern slides, was the first of three presented at the symposium.

† Chemotherapy Laboratories, Hoffmann-La Roche, Inc., Nutley, N. J.

* T. M. Reg. U. S. Pat. Office.

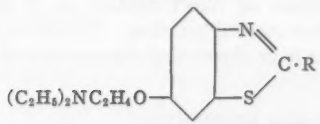
to twenty-one days at room temperature (21–24°C.). At the end of this period the fungus growth had covered the entire surface of the drug-free control plates. The growth on the medicated plates was measured and the figures thus obtained used to estimate the 50 per cent inhibiting concentration. Other methods of determination of activity were also used, of course, and will be described later in this paper.

TABLE 1 is meant to show the influence of different substitutions of the 2-amino

TABLE 1

FUNGISTATIC EFFECT OF BENZOTHIAZOLE DERIVATIVES

Plate method



R	*50% growth inhibiting concentration** *Trichophyton mentagrophytes*	*Microsporon lanosum*
$-CH_3$	50,000	3,000
$-N(CH_3)_2$†	2,000,000	800,000
$-NC_5H_{10}$	150,000	30,000
$-NC_4H_8O$	30,000	5,000
$-NC_9H_{10}$	250,000	40,000

* Reciprocals.
† Asterol.

group. It is evident that the dimethylamino compound represents an optimum effect, although the other derivatives appear appreciably active. Examples of this activity are the piperidine and tetrahydroquinoline compounds.

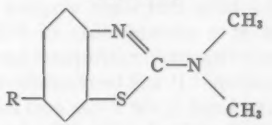
The effect of chemical variation of the substitution in the 6-position may be seen in TABLE 2. There is no doubt that the basic ether which characterizes Asterol is essential for the activity. The lower member of the series, the 6-dimethylaminoethoxy compound, is less active than Asterol. The isopropyl-compound is quite active, while the diethylaminodimethylpropoxy derivative shows a drop in activity once again. We might, therefore, summarize by saying that the properties of antifungal activity of this compound are determined as functions of the substitution in position 2 as well as in position 6.

As a rule, antifungal agents are biologically of the class of general antiseptics and exert their activity toward a comparatively wide spectrum of organisms. The activity of Asterol was specifically limited to the dermatophytes. The antibacterial effects

TABLE 2

FUNGISTATIC ACTIVITY OF BENZOTHIAZOLE DERIVATIVES

Plate method



R	*50% growth inhibiting concentration** *Trichophyton mentagrophytes*	*Microsporon lanosum*
$OC_2H_4N(CH_3)_2$	50,000	12,000
$OC_2H_4N(C_2H_5)_2$†	2,000,000	800,000
$OCH(CH_3)CH_2N(CH_3)_2$	250,000	50,000
$OCH_2C(CH_3)_2CH_2N(C_2H_5)_2$	64,000	50,000

* Reciprocals.
† Asterol.

TABLE 3

FUNGISTATIC ACTIVITY OF ASTEROL AGAINST COMMON MOLDS

Organism	*Amount of growth at 0.2%*	*controls*
Penicillium digitatum	++++	++++
Aspergillus flavus	++++	++++
Fusarium oxysporum	++++	++++
Botrytis poeaniae	++++	++++

of Asterol in dilution tests as well as in plate tests were negligible. Although gram-positive organisms appeared slightly more sensitive, the range of active concentration, 1–1000 to 1–2000, was almost 1000 times less than that observed with the dermatophytes.

Apathogenic fungi such as *Penicillium digitatum*, *Aspergillus flavus*, *Fusarium oxysporum*, and *Botrytis paeoniae* also proved to be highly resistant.

TABLE 3 shows that even a dilution of 1–500 was not able to inhibit the abundant

growth of the fungi. We might mention, however, that this growth was not typical. The occurrence of atypical growth will be discussed later in the paper.

We are aware that the four organisms included in these experiments represent, of course, only a small section of the large group of common molds or plant pathogens. Species or strains of higher sensitivity might be found if work is extended in this direction. Dermatophytes, on the other hand, were quite uniformly sensitive to Asterol. This can be seen in TABLE 4. Although one sees from this table that slight atypical growth appears at a concentration of 1–100,000, this is only true when microspores are used as the inoculum. It will be remembered that, in TABLES 1 and 2, the 50 per cent inhibiting concentration was 1–2,000,000 when a mat inoculum was employed.

TABLE 4

FUNGISTATIC ACTIVITY OF ASTEROL AGAINST DERMATOPHYTES

	Growth		
Dilution 1—	*Trichophyton mentagrophytes*	*Trichophyton purpureum*	*Microsporon audouini*
1000	0	0	0
10,000	0	0	0
100,000	+ (atypical)	+ (atypical)	+ (atypical)
Controls	++++	++++	++++

The high, specific fungistatic activity as demonstrated by the unusually low active concentration towards dermatophytes was not the only property of Asterol which made it appear interesting. The compound also had a high degree of diffusibility. This could be demonstrated in experiments where the drug, in the form of a carbowax ointment, was placed in a hole in the center of a Sabouraud's agar plate. The plates were previously seeded with a heavy spore suspension of *Trichophyton mentagrophytes* or *Microsporon lanosum*. There was sufficient diffusion into the agar from a 2.0 per cent carbowax ointment to give an area of inhibition of 128.0 cm.^{2} on petri dishes of 15 cm. diameter. A 0.2 per cent ointment on the same type of plates gave areas of inhibition of growth of approximately 70.0 cm.^{2}

It has been the experience of our laboratory, as well as that of others, that under the experimental conditions of the dilution test in a suitable liquid medium a higher sensitivity of microorganisms, bacteria as well as fungi, is found than by the agar plate method. This was not the case with Asterol. If this compound was tested against the microspores of the dermatophytes in Sabouraud's glucose broth containing graded concentrations of the compound, the values of complete inhibition were considerably lower than those that would be expected from the tests described on solid medium. If one considered partial inhibition and "atypical" growth, there was, of course, quite a close agreement between the two methods, but the fact of insufficient activity under the seemingly more favorable conditions of direct contact in a liquid medium was still puzzling. Special experiments have shown that the presence of the agar gel exerted an enhancing influence on the antifungal effect.

FIGURE 1 shows the results of an experiment in which increasing amounts of agar were added to Sabouraud's broth in which the dilution tests with Asterol were carried out. The inoculum consisted of 2,500,000 microspores and the tubes were kept in an incubator room at 28°C. The concentration required for complete inhibition, as represented by the drawn-out line, decreases gradually with the increasing concentration of agar until it reaches the concentration of 1–2,000,000 ($10^{-6.3}$) with a medium containing 0.8 per cent agar. This gel was already more than semi-solid at the incubator temperature. Partially inhibited atypical growth was present in the agar-free medium even at these low concentrations.

We do not have a satisfactory explanation for the phenomenon at the present time. It was first hypothesized that the

effect of Asterol might be dependent on a certain colloidal state of the medium. The fact that the effect towards other organisms, *e.g.*, bacteria or common molds, was not

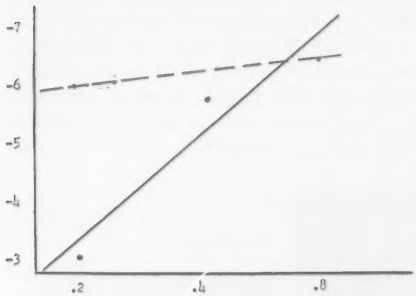


FIGURE 1. Effect of agar on the fungistatic activity of Asterol.

equally influenced by the presence of agar in the medium makes this interpretation appear improbable. Other gels, such as methyl cellulose, cellosize, and gelatine, also failed to give a similar enhancement. This leaves the possibility that the galacturonic acid of the agar might play a role in this phenomenon.

Atypical growth under the influence of Asterol has frequently been mentioned in this paper. We should like to elaborate on this property of the new compound because it seems to be specific for this substance and has not been observed with any of the many hundreds of new compounds from many chemical groups which were tested during the last ten years. Atypical growth is generally observed in the presence of low concentrations of Asterol, concentrations which are not sufficient to suppress growth completely. Culturally on agar, atypical colonies appear dry and yeastlike, forming small colonies of buff to yellow color. Characteristic of this growth is complete absence of aerial mycelia. Microscopically, the appearance of the fungus is fundamentally changed. Instead of the familiar picture of dense mycelial strands, one finds, almost completely, only chlamydospores.

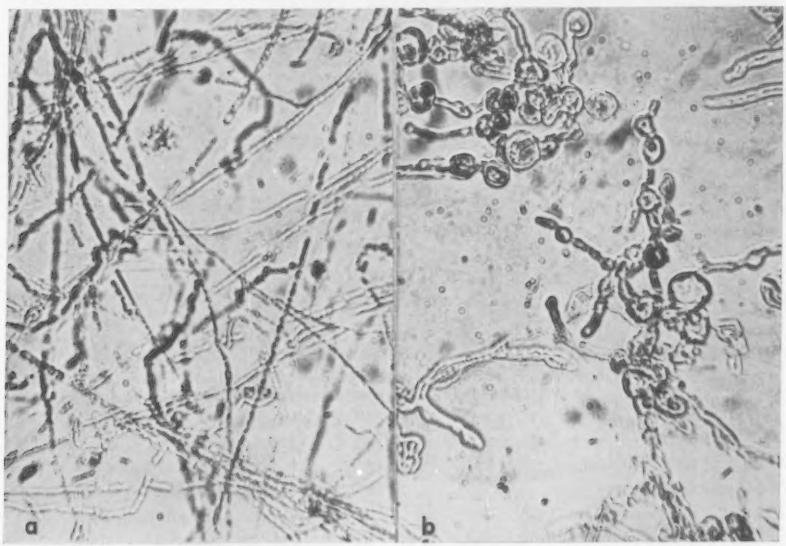


FIGURE 2. (a) Normal mycelial growth of *Microsporon audouini*—oil immersion—eyepiece 6X. (b) Chlamydospore formation of *Microsporon audouini* under the influence of Asterol—same magnification.

FIGURE 2 depicts the normal and atypical microscopic appearance of *Microsporon audouini*. We have observed similar changes with *Trichophyton mentagrophytes*. Common molds such as *Aspergillus, Peni-*

cillium, and *Fusarium* responded to higher concentrations of Asterol with excessive formation of arthrospores or chlamydospores.

In previous tables, we have stressed the point of active concentrations, although the fact of atypical growth has been mentioned. Partial inhibition and atypical growth can be seen only with considerably lower concentrations of Asterol and were observed with all the dermatophytes included in our tests. The examples which we are going to present in the following figure used *Trichophyton purpureum*.

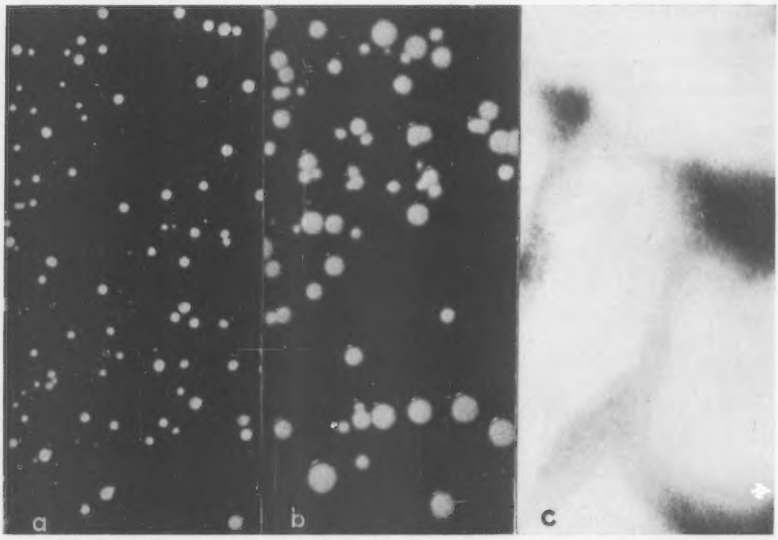


FIGURE 3. (a) Dwarf colonies of *Trichophyton purpureum* under the influence of Asterol, 1–100,000. (b) Atypical, small colonies of *Trichophyton purpureum* under the influence of Asterol, 1–1,000,000. (c) Normal colony growth of *Trichophyton purpureum*.

FIGURE 3a shows the very small and atypical colonies which developed at a concentration of 1–100,000 Asterol and which also showed the microscopic changes just mentioned. Approximately the same type of picture was observed at a concentration of 1–1,000,000 Asterol, although the colonies appeared somewhat larger, and on close examination one could see the beginning of aerial mycelial growth (FIGURE 3b). How much the natural development of the fungus is suppressed by the low concentrations is evident from FIGURE 3c, which shows normal mycelial growth of the strain used in this experiment. At this point, it might be appropriate to mention that the atypical growth was not an irreversible mutation, since transferring an atypical colony to plain Sabouraud's agar resulted in the growth of normal colonies.

Another quite interesting modification of *Trichophyton purpureum* by Asterol concerns the pigment formation. This characteristic function of the fungus can be influenced by metabolic changes. The influence which different sugars have is known through the papers of Lewis and Hopper[10] and Bocobo and Benham.[11] These authors reported, and we have confirmed the results with ten strains, that the pigment normally used for the identification of *Trichophyton purpureum* is formed when glucose is used for the carbohydrate source but is completely absent when maltose is substituted as the carbohydrate source.

In media containing low concentrations of Asterol, pigment formation appears impaired even if fairly normal growth is obtained. In FIGURE 4, cultures of *Trichophyton purpureum* on Sabouraud's agar containing glucose are shown after three weeks incubation. The tubes contain varying concentrations of Asterol. FIGURE 4a shows the appearance of the growth on the surface and indicates that more or less extensive development of the fungus began at a concentration of 1–1,000,000 and gradually increased to the more confluent growth seen in the control tubes. FIGURE 4b shows an identical experiment done at the same time and photographed from the back of the tubes in order to demonstrate the pigment formation. It is quite evident that, even at as low a concentration as 1–8,000,000, little or no pigment is formed. At a concentration of 1–16,000,000, which can hardly be considered true growth inhibition, the characteristic function of pigment formation is still partially suppressed. We have tentatively assumed that the effect of Asterol might involve an interference with the carbohydrate metabolism of the fungi.

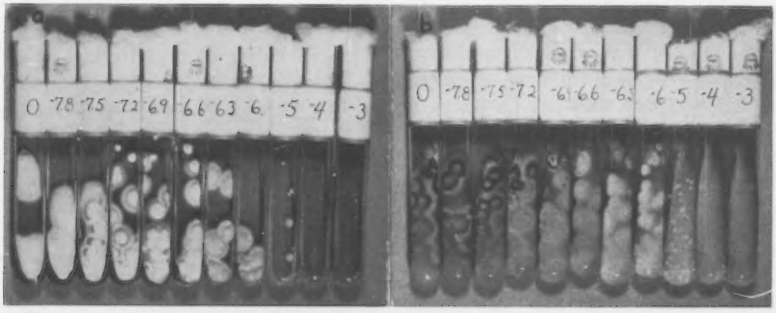


FIGURE 4. Fungistatic experiment showing the effect of various concentrations of Asterol on the pigment production of *Trichophyton purpureum:* (a) front view; (b) back view.

Summary. In this paper, the results of part of our studies with benzothiazole derivatives and their antifungal activity have been presented. Some of the more characteristic properties of one specific compound, Asterol, have been described because they appear unusual. We would like to characterize Asterol as a new antifungal agent of low toxicity and good solubility and diffusibility in agar gels. Its fungistatic effect, which is specific against different dermatophytes, is appreciably high and, even at concentrations too low to prevent fungal growth, it still exerts modifying functions on the morphology and metabolism of the microorganisms. We are only too well aware that we have presented *in vitro* experiments, the results of which are meaningful only in connection with clinical data. The practical value of Asterol was found and decided upon during its clinical investigation.

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ANTISPORULATING EFFECT OF ASTEROL DIHYDROCHLORIDE*

By FREDERICK REISS†‡

Despite the intense interest displayed by public health agencies in the welfare of school children, the incidence of tinea capitis remains rather high. Thus, of 1,840 patients referred in the last four years to the Section of Mycology of the Dermatologic Outpatient Service of Bellevue Hospital, 458 were children afflicted with ringworm of the scalp.

At an early stage of our clinical trials with the antifungal compound synthesized by Dr. Steiger and tested *in vitro* by Drs. Schnitzer and Grunberg,[1] we were impressed with the rapidity with which diminution of fluorescence was accomplished in many patients with tinea capitis. Therefore, it seemed worthwhile to investigate, in the laboratory, the response of *Microsporon audouini* infected hairs to spraying with the new drug,§ as gauged by cultural findings and by the appearance of the hairs under Wood's Light. Furthermore, the thought suggested itself that, if Asterol Dihydrochloride was effective in eliminating viable spores from the carriers, then the drug might be successfully employed for prophylactic purposes, for example, in motion-picture theatres, where infected hairs, adhering to the seats, are reputed to be a potential source of disseminating the disease.

Method and Material. Hair infected with *Microsporon audouini* was collected under Wood's Light from untreated children afflicted with tinea capitis. The hairs, divided in the desired batches, were implanted on plush placed in petri dishes. Excluding one control, eight experiments were set up. Four petri dishes were sprayed with a 2 per cent solution of Asterol Dihydrochloride and four with a Decupryl solution as it is available commercially. The spraying schedules were the same for both preparations, namely, 5 times weekly, 3 times weekly, twice weekly, and once weekly for one petri dish each. Spraying was initiated on all eight dishes on the first day and, on all subsequent days with the exception of Saturdays and Sundays, the hairs were examined under Wood's Light for three weeks. Similarly, with the exception of Saturdays and Sundays, attempts were made daily for three weeks to culture organisms from each dish.

Findings. It appears from TABLE 1, which records our findings, that all four dishes sprayed with Asterol Dihydrochloride were culturally negative and remained so after one single spraying. Contrariwise, all four dishes remained culturally positive after one spraying with Decupryl. The hairs sprayed with Decupryl were rendered culturally negative only after three consecutive daily sprayings and, on the petri dish sprayed three times weekly, the cultures were without growth only after a total of eight sprayings, or well in the third week of the experiment. Spraying with Decupryl twice weekly and once weekly was never productive of negative cultural findings.

The examinations under Wood's Light showed that complete disappearance of fluorescence was accomplished with Asterol Dihydrochloride on two spraying schedules, namely, five times weekly and three times weekly. On the former, there was complete absence of fluorescence after seven treatments (tenth day of the experiment) and on the latter there was complete absence of fluorescence after eight treatments (eighteenth day of the experiment). Wood's Light examination remained negative then until the twenty-second day of the experiment in both instances.

Contrariwise, with Decupryl, there was never any change in the amount of fluorescence, regardless of the spraying schedule or duration of treatment.

Discussion. The disappearance of

* On October 27, 1950, the Division of Mycology held a symposium on "Studies With a New Benzothiazole Derivative." This paper, illustrated with lantern slides, was the second of three presented at the symposium.

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‡ With the technical assistance of Doris Winston.

§ Supplied by Hoffmann-La Roche Inc. initially under the code designation Ro2-2453 and later under the name of Asterol Dihydrochloride.

TABLE 1

RESPONSE OF *Microsporon Audouini*-INFECTED HAIRS, IMPLANTED ON THEATRE SEAT MATERIAL IN PETRI DISHES, TO SPRAYING WITH TWO PER CENT ASEROL DIHYDROCHLORIDE (RO2-2453) AND DECUPRYL, RESPECTIVELY

	Control			*RO2-2453*														*Decupryl*											
Days	*Spray.*	*W.L.**	*Cult.*	*W.L.*	*Cult.*	*Spray. 5× weekly*	*W.L.*	*Cult.*	*Spray. 3× weekly*	*W.L.*	*Cult.*	*Spray. 2× weekly*	*W.L.*	*Cult.*	*Spray. 1× weekly*	*W.L.*	*Cult.*	*Spray. 5× weekly*	*W.L.*	*Cult.*	*Spray. 3× weekly*	*W.L.*	*Cult.*	*Spray. 2× weekly*	*W.L.*	*Cult.*	*Spray. 1× weekly*
1	−					x			x			x			x			x			x			x			x
2	−	+	+		+	− x		+	−		+	−		+	−	+	+	x	+	+	x	+	+	x	+	+	
3	−	+	+		+	− x		+	− x		+	−		+	−	+	+	x	+	+	x	+	+		+	+	
4	−	+	+		+	− x		+	−		+	− x		+	−	+	−	x	+	+		+	+	x	+	+	
5	−	+	+	most	+	− x		+	− x		+	−		+	−	+	−	x	+	+	x	+	+		+	+	
6																											
7																											
8	−	+	+	1/2	+	− x	most	+	− x	most	+	− x		+	− x	+	−	x	+	+	x	+	+	x	+	+	x
9	−	+	+	most	−	− x	1/2	+	−	2/3	+	−	2/3	+	−	+	−	x	+	+		+	+		+	+	
10	−	+	+		−	− x	1/2	+	− x	2/3	+	−	2/3	+	−	+	−	x	+	+	x	+	+		+	+	
11	−	+	+		−	− x	most	−	−	3/4	+	− x	most	+	−	+	−	x	+	+		+	+	x	+	+	
12	−	+	+		−	− x	most	−	− x	most	−	−	most	+	−	+	−	x	+	+	x	+	+		+	+	
13																											
14																											
15	−	+	+		−	− x	1/2	−	− x	most	−	− x	3/4	+	− x	+	−	x	+	+	x	+	+	x	+	+	x
16	−	+	+		−	− x	most	−	−	3/4	+	−	3/4	+	−	+	−	x	+	+		+	+		+	+	
17	−	+	+		−	− x	most	−	− x	1/2	+	−	1/2	−	−	+	−	x	+	+	x	+	+		+	+	
18	−	+	+		−	− x		−	−	3/4	−	− x	3/4	−	−	+	−	x	+	−		+	+	x	+	+	
19	−	+	+		−	− x		−	− x	3/4	−	−	3/4	−	−	+	−	x	+	−	x	+	+		+	+	
20																											
21																											
22	−	+	+		−	−		−	−	3/4	−	−	3/4	−	−	+	−		+	−		+	+		+	+	

* W. L. = Wood's Light

fluorescence of Asterol-treated hairs, which does not result from spraying with Decupryl, is indicative of a greater penetrating power or a greater antifungal activity of the former drug. Asterol Dihydrochloride not only rendered the hairs Wood's Light negative, but it also altered the quality of the fluorescence in that the hairs showed a dullness of fluorescence as early as on the fourth day of the experiment. Such changes were not observed with Decupryl.

Far more significant, however, is the fact that even a single exposure of infected hairs to 2 per cent Asterol Dihydrochloride resulted in an absence of growth in the culture and, of course, more frequent exposures yielded the same results. Spraying with Decupryl once weekly or even twice weekly was not productive of inhibiting the growth of *Microsporon audouini* at any time during the course of the experiment: a period of 22 days. Spraying with Decupryl 3 times weekly did not produce a negative culture until the 18th day of the experiment, and three consecutive daily sprayings with Decupryl were required to obtain a negative culture.

While there is evidence of antifungal activity of Decupryl, there can be no doubt on the basis of the results obtained in the experiments here described that Asterol Dihydrochloride is the superior agent.

In view of our laboratory findings, we have made extensive use of 2 per cent and later of 5 per cent Asterol Dihydrochloride in the treatment of tinea capitis. The good results obtained in 100 cases, to be described elsewhere, were achieved by treating vigorously the infected areas of the scalp and at the same time spraying the noninfected areas of the scalp as well as the skull caps. With this regimen we have not seen spreading of the infection to healthy parts of the scalp, a previously not uncommon observation.

In a sense, our initial objective was to prevent auto-infection, with subsequent eradication of the offending fungi. The former can be easily achieved, because one single exposure of *Microsporon audouini* infected hairs to 2 per cent Asterol Dihydrochloride results in the suppression of sporulation. The same would presumably apply to *Microsporon audouini*-infected hairs adhering to theatre seats if the plush were sprayed with an Asterol Dihydrochloride solution. The role of theatre seats in transferring tinea capitis is a moot question. Yet, Behling and Markel[2] found 20 seats out of 200 contaminated with infected hairs from which *Microsporon audouini* could be cultured. Similarly, Schwartz[3,4] recognized contaminated seats as a potential source of infection. In combating the epidemic in Hagerstown, he suggested, among other measures, that all theatre managers "have the seats, especially the backs, vacuumed at least once a day." On the basis of our experiments, we anticipate spraying of the seats with Asterol Dihydrochloride to be a more effective procedure.

We are aware of the fact that the observations made do not permit a definite statement as to the sporicidal effect of Asterol Dihydrochloride, because the active agent was not removed from the carrier. Rinsing of the hairs after their exposure to either of the two agents studied and before placing them on Sabouraud's agar slants was purposely omitted so that the effect of the drug could be investigated under conditions simulating those in motion picture theatres.

Summary and Conclusions. Hairs extracted from children afflicted with tinea capitis of the *Microsporon audouini* type were sprayed on petri dishes with a 2 per cent solution of Asterol Dihydrochloride on the one hand and with Decupryl on the other.

Evidence is presented that one Asterol Dihydrochloride spraying of hairs infected with *Microsporon audouini* suppresses sporulation.

On account of the high antisporulating index of Asterol Dihydrochloride, it is recommended that, in the treatment of tinea capitis also, noninfected areas of the scalp should be sprayed daily in order to prevent the spread of the infection. Simi-

larly, skull caps should be sprayed with the drug.

The suggestion is made that the seats of motion picture theatres which are frequented by school children should be sprayed with Asterol Dihydrochloride as a prophylactic measure.

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TREATMENT OF SUPERFICIAL FUNGUS INFECTIONS WITH A NEW ANTIFUNGAL AGENT*

By CONRAD STRITZLER,† IRVING M. FISHMAN,‡ AND STEPHEN LAURENS‡

The large number of antifungal agents in use today is ample evidence that there is no preparation which can be considered completely satisfactory for the treatment of the great majority of patients with superficial fungus infections. The merits of fatty acid compounds, chiefly undecylenic acid and propionic acid, have been widely discussed and their field of usefulness delineated,[1a, b] but the ideal antifungal agent has yet to be found.

The attributes of a good antifungal agent may be considered to be the following: (1) It should have a broad antifungal spectrum, *in vivo*, chiefly against dermatophytes of the genera *Trichophyton* and *Microsporon*, and against *Candida albicans*. (2) It should not be an irritant or potent sensitizing agent in effective concentration. (3) It should have a mild keratolytic or penetrant effect so that it can reach the site of infection.

In vitro studies by Grunberg and his associates[2] indicate that the dihydrochloride of 2-dimethylamino-6-(beta-diethyl-aminoethoxy)-benzothiazole, hereafter called Asterol Dihydrochloride,* is a potent fungistatic agent, especially on dermatophytes of the genera *Trichophyton* and *Microsporon*. Since the new compound seemed to have greater activity, *in vitro*, than a widely used antifungal preparation, we set out to investigate its clinical merits.

Prophetic patch tests on two hundred subjects with ointment, tincture, and dusting powder, all containing 2 per cent Asterol Dihydrochloride, showed no evidence of primary irritation at the end of 48 hours. These same 200 persons did not show a positive reaction when retested two weeks later. Similarly, 100 patients who had previously been treated with 2 per cent Asterol Dihydrochloride were patch tested with a 5 per cent preparation, and again no positive reaction was obtained. All of 10 patients patch tested with 10 per cent Asterol Dihydrochloride, however, showed a 1 plus or 2 plus reaction. This indicated that Asterol Dihydrochloride in concentrations of 2 and 5 per cent is not a primary irritant or potent sensitizer, but that the 10 per cent concentration is a primary irritant.

While the value of prophetic patch tests is limited, the 2 per cent preparations were in use for more than six months on several hundred patients with no evidence of sensitization in a single case. The 5 per cent preparations have been in use on more than 150 patients since July, 1950. One of these developed contact dermatitis, but she was found to be sensitive to the carbowax 1500 base, and not to Asterol Dihydrochloride. Two patients developed profuse

* On October 27, 1950, the Division of Mycology held a symposium on "Studies With a New Benzothiazole Derivative." This paper, illustrated with lantern slides, was the third of three presented at the symposium.

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* Supplied by Hoffmann-La Roche Inc., Nutley, N. J.

desquamation of the soles and interdigital spaces of the toes following the use, for two weeks, of 5 per cent tincture and 5 per cent ointment. These reactions subsided when the 5 per cent dusting powder was substituted. Subsequent patch tests proved negative. We do not know the cause of these reactions.

The effectiveness of Asterol Dihydrochloride was studied in the superficial fungus infections listed in TABLE 1.

TABLE 1
CLINICAL FORMS OF SUPERFICIAL MYCOSES TREATED WITH ASTEROL DIHYDROCHLORIDE

Infection	*Causative organism*
Tinea Capitis	*M. audouini* *M. lanosum* *T. gypseum*
Tinea Corporis	*T. purpureum* *T. gypseum* *M. lanosum*
Tinea Cruris	*T. purpureum* *T. gypseum* *C. albicans*
Tinea Pedis	*T. purpureum* *T. gypseum* *C. albicans*
Paronychia and Onychia	*C. albicans*
Erosio Interdigitalis Blastomycetica	
Tinea Versicolor	
Erythrasma	

At first, 2 per cent Asterol Dihydrochloride was used. This proved effective in tinea capitis due to *Microsporon audouini* and *Microsporon lanosum*, and in tinea versicolor and monilial infections, but it was not effective in *Trichophyton purpureum* and *Trichophyton gypseum* infections. Subsequently, preparations containing 5 per cent Asterol Dihydrochloride were employed, and these were found to be effective in *Trichophyton purpureum* and *Trichophyton gypseum* infections.

Tinea Capitis. Our preliminary results with 2 per cent Asterol Dihydrochloride in the treatment of tinea capitis were summarized in a previous paper.[3] Of the cases presented, 64 patients, who had had no previous Roentgen-ray therapy, have since been followed further and 19 cases added.

The following regimen has been employed: The hair is clipped short initially and subsequently every seven to ten days. The scalp is shampooed every other day. Paper caps are worn under cloth caps, the former being burned and the latter boiled daily. Asterol Dihydrochloride Tincture is sprayed over the entire scalp every morning and rubbed in with a soft tooth brush, moistened with the liquid. The ointment is applied in a similar manner at night. We have recently changed to 5 per cent Asterol Dihydrochloride also in the treatment of tinea capitis, since the higher concentration is equally safe and is attended by a more rapid response. Mothers are instructed to remove obviously infected hairs manually, and weekly manual epilation is performed by the dermatologist. (Kligman[4] doubts the rationale of manual epilation, although the value of this procedure has been stressed by others.[5])

Six consecutive weekly Wood's Light examinations were arbitrarily chosen as a criterion of cure. Subsequently, all patients were examined at monthly intervals for three months and were not discharged until the third monthly re-examination proved negative. Treatment was usually discontinued after the third negative Wood's Light examination. TABLE 2 summarizes our results to date.

Patients whose hair became nonfluorescent under filtered light, but who have not been negative for six consecutive weeks, are not listed as cured. They are grouped together in the column "Wood's Light negative." In approximately two-thirds of the cases, six to twelve weeks were required for the first negative Wood's Light examination, with the rest requiring less than six or over twelve weeks of treatment.

As is seen, the overall cure rate is 60 per cent, with the incidence of cure being greater in the group with *Microsporon lanosum* infections. The cure rate among the *Micro-*

sporon audouini cases is 55.7 per cent, with an additional 14.7 per cent having been rendered Wood's Light negative.

It will be noted that 20, or 32.8 per cent, of the 61 cases of anthropophilic tinea capitis developed an inflammatory reaction during treatment. In our experience, only a few patients previously treated with other antifungal agents developed such a reaction. When we changed to 5 per cent Asterol Dihydrochloride, the incidence of inflammatory reactions became lower. This observation seemed to invalidate the original suspicion that the inflammatory reactions were caused by Asterol Dihydrochloride. The *Trichophyton* skin test remained negative in two out of 10 cases tested, the other eight becoming positive with the onset of inflammation. It is suggested that the inflammatory reaction is predicated on an altered immune-biologic response of the host to the parasite. The problem is so complex that we are not prepared to offer an explanation at this time. It is apparent, however, that the appearance of these reactions complicates the problem of evaluating the merits of any therapy enormously, since patients go on to a relatively rapid cure once inflammation supervenes. The incidence of inflammatory reactions in the group of patients presented is unusually high, but similar figures have been reported by Scully, Livingood, and Pillsbury.[6]

In our hands, Asterol Dihydrochloride has been more effective in ringworm of the scalp than any other topical agent we have tried. In order to determine the merits of Asterol Dihydrochloride conclusively, however, we recently decided to use the 5 per cent Asterol Dihydrochloride preparations in one half of our cases, every other case being treated with non-medicated tincture and ointment bases whose pH has been adjusted to that of the medicated products. So far, 20 patients have been included in this program. Of 10 children treated with Asterol Dihydrochloride preparations for one month, one became Wood's Light negative, four showed diminished fluorescence, and five no change. In none of the 10 controls treated over the same period of time has there been any improvement so far. This suggests, but does not prove, that the antifungal agent, rather than pH, time, or vehicle, is responsible for the clinical results.

A larger number of cases will be followed on placebo therapy for a longer period of time in order to settle this point. Kligman[7] has recently stressed the importance of this type of control in evaluating topical therapy in tinea capitis. Cipollaro and Brodey[8] have recently discussed the failure of topical therapy and the necessity for X-ray epilation in the anthropophilic type of tinea capitis. Robinson[9] and Mitchell[10] have demonstrated the resistance of *Microsporon audouini* infection of the hair *in vitro* to the action of various antifungal agents. Reiss,[11] however, showed that a single spraying with Asterol Dihydrochloride suppresses sporulation of hairs infected with *Microsporon audouini*.

We feel that our results are sufficiently encouraging to warrant a more optimistic attitude toward topical therapy in this disease. During the past year, we have not found it necessary to treat a single case by Roentgen-ray epilation, although it now

TABLE 2

TINEA CAPITIS TREATED WITH ASTEROL DIHYDROCHLORIDE
CASES WITHOUT PREVIOUS X-RAY TREATMENT

Offending organisms	*Number of patients*	*Cured*	*Wood's Light negative*	*Improved (diminution of fluorescence)*	*Not improved*	*Inflammatory reaction*
Microsporon audouini	61	34	9	14	4	20
Microsporon lanosum	21	16	4	1	–	12
Tricophyton gypseum	1	–	–	1	–	1
Total	83	50	13	16	4	33

appears that a small number of patients will require this procedure.

Tinea of the Glabrous Skin and of the Nails. As was previously mentioned, results with a preparation containing two per cent Asterol Dihydrochloride were unsatisfactory in infections due to *Trichophyton purpureum* and *Trichophyton gypseum*. The following discussion, unless otherwise stated, concerns our findings and observations with materials containing five per cent of the antifungal agent. Only patients with positive cultures are included in the evaluation.

TABLE 3
TINEA CORPORIS TREATED WITH FIVE PER CENT ASTEROL DIHYDROCHLORIDE

Causative organism	*Number of patients*	*Number cured*	*Number improved*	*Number unimproved*
T. purpureum	17	5	10	2
T. gypseum	16	6	9	1
M. lanosum	2	1	1*	–
Total	35	12	20	3

* Period of treatment only two weeks.

Tinea Cruris. As is seen from TABLE 4, 22 cases with tinea cruris were treated with Asterol Dihydrochloride. In most instances, the ointment was applied at night, the dusting powder being used in the morning. The medication was tolerated well. Clinical cures were obtained in four to six weeks in 13 patients, or 59.1 per cent, and eight patients, or 36.3 per cent, were improved. Some of the infections caused by *Candida albicans* responded almost dramatically.

Tinea Pedis. TABLE 5 shows our results with Asterol Dihydrochloride in tinea pedis. Acute and pyodermic phases were treated with soaks of Burow's solution (1:30) or with a solution of potassium permanganate (1:10,000) until the acute process subsided. Thereafter, Asterol Dihydrochloride Tincture was used during the day and the ointment at night. The dusting powder was sprinkled into the socks and shoes to keep the feet dry and prevent a recurrence. The period of treatment was

TABLE 4
TINEA CRURIS TREATED WITH FIVE PER CENT ASTEROL DIHYDROCHLORIDE

Causative organism	*Number of patients*	*Number cured*	*Number improved*	*Number unimproved*
Tricophyton purpureum	12	5	6	1
Tricophyton gypseum	6	4	2	–
Candida albicans	4	4	–	–
Total	22	13	8	1

Tinea Corporis. TABLE 3 shows the distribution of causative organisms in our group of 35 patients with tinea corporis and the results obtained. In most cases, Asterol Dihydrochloride Ointment was applied twice daily. The period of treatment ranged from four to six weeks. Twelve patients, or 34.2 per cent, were cured and 20, or 57.1 per cent, were improved. Patients listed as cured were clinically cured cases. Post-treatment scrapings and cultures were not done. An inflammatory reaction akin to that observed in the majority of the tinea capitis cases caused by this organism occurred in both patients whose infection was due to *Microsporon lanosum*.

two to six weeks. Of the 41 cases included in this group, 25, or 60.9 per cent, were cured and 14, or 34.1 per cent, were improved. In general, results were at least as good as with undecylenic acid preparations, but cases due to *Candida albicans* responded better to Asterol Dihydrochloride.

Tinea Versicolor and Erythrasma. TABLE 6 summarizes our results with Asterol Dihydrochloride in tinea versicolor and in erythrasma. In several of the 18 cases with tinea versicolor, examination under Wood's Light disclosed much more widespread involvement than was clinically evident. The Asterol Dihydrochloride Ointment was, therefore, applied from the neck to the toes after a soap and water

scrub every night. All patients were cured in seven to ten days, the scale disappearing and scrapings and Wood's Light examinations becoming negative. Asterol Dihydrochloride dusting powder was used in an effort to prevent relapse or reinfection. Achromia parasitica, where present, persisted however, after cure of the active infection.

TABLE 5

TINEA PEDIS TREATED WITH FIVE PER CENT ASTEROL DIHYDROCHLORIDE

Causative organism	*Number of patients*	*Number cured*	*Number improved*	*Number unimproved*
Trichophyton purpureum	16	7	7	2
Trichophyton gypseum	19	12	7	–
Candida albicans	6	6	–	–
Total	41	25	14	2

TABLE 6

TINEA VERSICOLOR TREATED WITH FIVE PER CENT ASTEROL DIHYDROCHLORIDE

Causative organism	*Number of patients*	*Number cured*	*Number improved*	*Number unimproved*
Microsporon furfur	18	18	–	–

ERYTHRASMA TREATED WITH FIVE PER CENT ASTEROL DIHYDROCHLORIDE

Causative organism	*Number of patients*	*Number cured*	*Number improved*	*Number unimproved*
Microsporon minutissimum	1	1	–	–

TABLE 7

PARONYCHIA AND ONYCHIA TREATED WITH FIVE PER CENT ASTEROL DIHYDROCHLORIDE

Causative organism	*Number of patients*	*Number cured*	*Number improved*	*Number unimproved*
Candida albicans	18	12	4	2*

* Period of treatment only two weeks.

EROSIO INTERDIGITALIS BLASTOMYCETICA TREATED WITH FIVE PER CENT ASTEROL DIHYDROCHLORIDE

Causative organism	*Number of patients*	*Number cured*	*Number improved*	*Number unimproved*
Candida albicans	14	6	8	–

One patient with erythrasma of the axillae was cured after two weeks of treatment with Asterol Dihydrochloride Tincture.

Paronychia and Erosio Interdigitalis Blastomycetica. TABLE 7 shows our results with Asterol Dihydrochloride in paronychia caused by *Candida albicans* and in erosio interdigitalis blastomycetica.

The 18 patients with paronychia were treated with the liquid preparation. The tincture was applied with a cotton-tipped applicator twice daily, care being taken to apply the preparation well under the nail folds as well as on the surface of the involved areas. Twelve patients, or two-thirds of the cases, were clinically cured in four to six weeks, four were improved, two unimproved. The latter cases, however, have been under treatment for only two weeks. Occasional application of the tincture was advised after a clinical cure had been attained, to prevent relapse or recurrence. Patients with paronychia due to *Candida albicans* make more rapid progress with Asterol Dihydrochloride than with any other medication previously used, including permanganate soaks, Castellani's paint, undecylenic acid preparations, and ammoniacal silver nitrate.

Erosio interdigitalis caused by *Candida*

albicans also responded well. Six of the 14 cases were cured in four to six weeks. The other eight improved but were not cured after one month of treatment.

Comment. Asterol Dihydrochloride is the most effective topical remedy for the treatment of tinea capitis of the *Microsporon audouini* type we have used to date. We realize that the relatively high incidence of inflammatory reactions may have influenced our results, yet we are still scoring over 50 per cent cures within three months, although the occurrence of inflammatory reactions has decreased considerably. Rigid adherence to the technic outlined is considered essential.

Tinea of the glabrous skin appears to respond as well to five per cent Asterol Dihydrochloride as to undecylenic preparations, as reported by Hopkins and associates.[12]

It seemed of interest to determine the overall results obtained in combating the individual organisms causing mycotic infections of the glabrous skin and the nails in our series, regardless of the site of infection. Such an analysis is presented in TABLE 8, listing the original results with two per cent Asterol Dihydrochloride and the findings with the five per cent preparations. It becomes immediately evident that much better results were obtained with the five per cent preparations, particularly in infections due to *Trichophyton gypseum* and *Tricophyton purpureum*. *Candida albicans* infections also responded more favorably to the higher concentration. In general, results in tinea versicolor and in monilial infections were better with five per cent Asterol Dihydrochloride than with fatty acid preparations. Fungus infections due to *Tricophyton gypseum* and *Tricophyton purpureum* responded as well to five per cent Asterol Dihydrochloride as to undecylenic acid preparations. We have employed Asterol Dihydrochloride not only in the cases presented but also in a sizable group of patients for whom the causative organisms were not determined. Thus, our trials comprise well over 500 patients. On the basis of this experience, we think that Asterol Dihydrochloride has at least the first two attributes mentioned in the introduction of this paper as requisites of a good antifungal agent: it is distinguished by a broad antifungal spectrum, *in vivo*, and by good cutaneous tolerance. We have not undertaken trials to determine the keratolytic or penetrant effect of the drug, but the

TABLE 8

COMPARATIVE RESULTS WITH TWO PER CENT ASTEROL DIHYDROCHLORIDE AND FIVE PER CENT ASTEROL DIHYDROCHLORIDE IN MYCOSES OF THE GLABROUS SKIN AND THE NAILS

Offending organism	*2% Asterol Dihydrochloride*				*5% Asterol Dihydrochloride*			
	Number of patients	*Results*			*Number of patients*	*Results*		
		cured	*improved*	*not improved*		*cured*	*improved*	*not improved*
Trichophyton gypseum	68	11 (16.2%)	45 (66.2%)	12 (17.6%)	41	22 (53.7%)	18 (43.9%)	1 (2.4%)
Trichophyton purpureum	56	8 (14.2%)	24 (42.9%)	24 (42.9%)	45	17 (37.7%)	23 (51.1%)	5 (11.2%)
Candida albicans	36	13 (36.1%)	22 (61.1%)	1 (2.8%)	42	28 (66.6%)	12 (28.5%)	2* (4.9%)
Microsporon furfur	14	14 (100%)	—	—	18	18 (100%)	—	—
Microsporon lanosum	4	4 (100%)	—	—	2	1 (50%)	1* (50%)	—
Microsporon minutissimum	1	1 (100%)	—	—	1	1 (100%)	—	—
Total	179	51 (28.5%)	91 (50.8%)	37 (20.7%	149	87 (58.4%)	54 (36.2%)	8 (5.4%)

* Period of treatment only two weeks.

often rapid results indicate that it easily reaches the site of infection.

Conclusions. Asterol Dihydrochloride employed in accordance with the technic outlined is an effective topical remedy for the treatment of ringworm of the scalp caused by *Microsporon audouini* or *Microsporon lanosum.*

Five per cent Asterol Dihydrochloride is also useful in the treatment of the following superficial fungus infections: tinea corporis, tinea cruris, tinea pedis, tinea versicolor, paronychia caused by *Candida albicans*, and erosio interdigitalis blastomycetica. Monilial infections and tinea versicolor respond more favorably than to other medications.

Acknowledgment

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B. Elected October 26, 1950

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ACTIVE MEMBERSHIP

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Budzinsky, Nina, B.A., Bioche istry. Ass't to Director of Research, New York, N. Y.

Ceriotti, Giovanni, M.D., Biochemistry. Research Fellow, Sloan-Kettering Inst. for Cancer Research, New York, N. Y.

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